Psychological profiles after percutaneous coronary intervention

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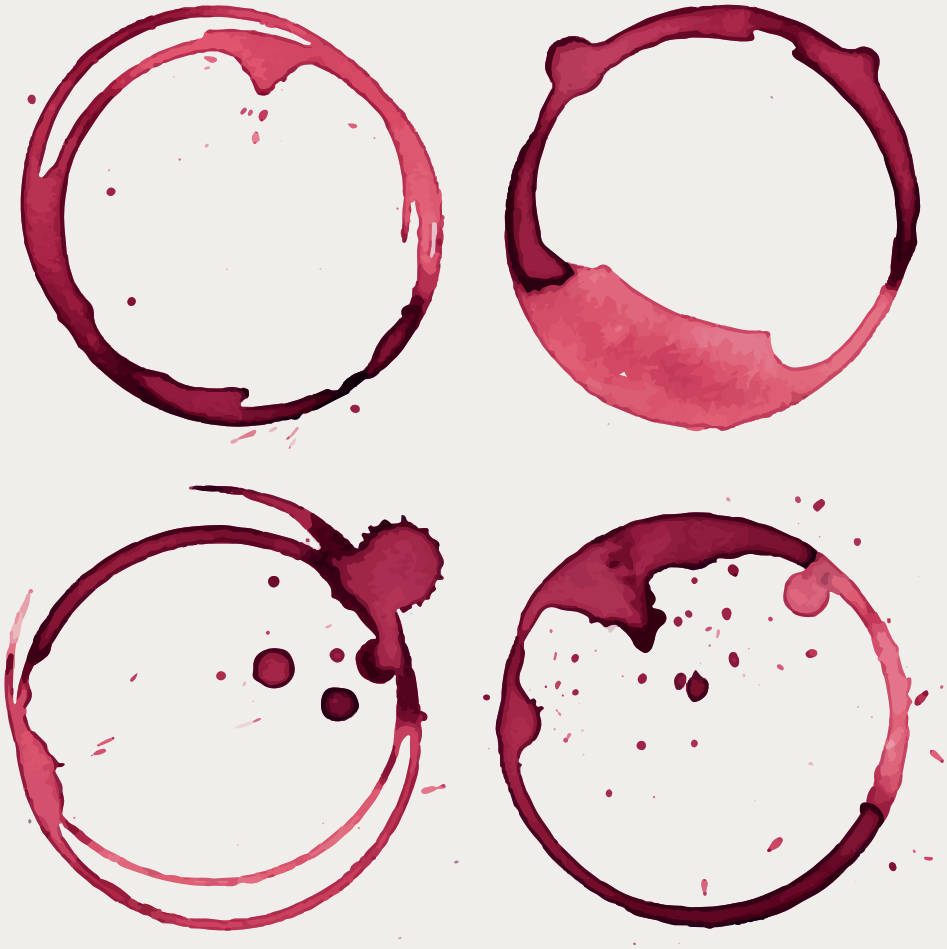

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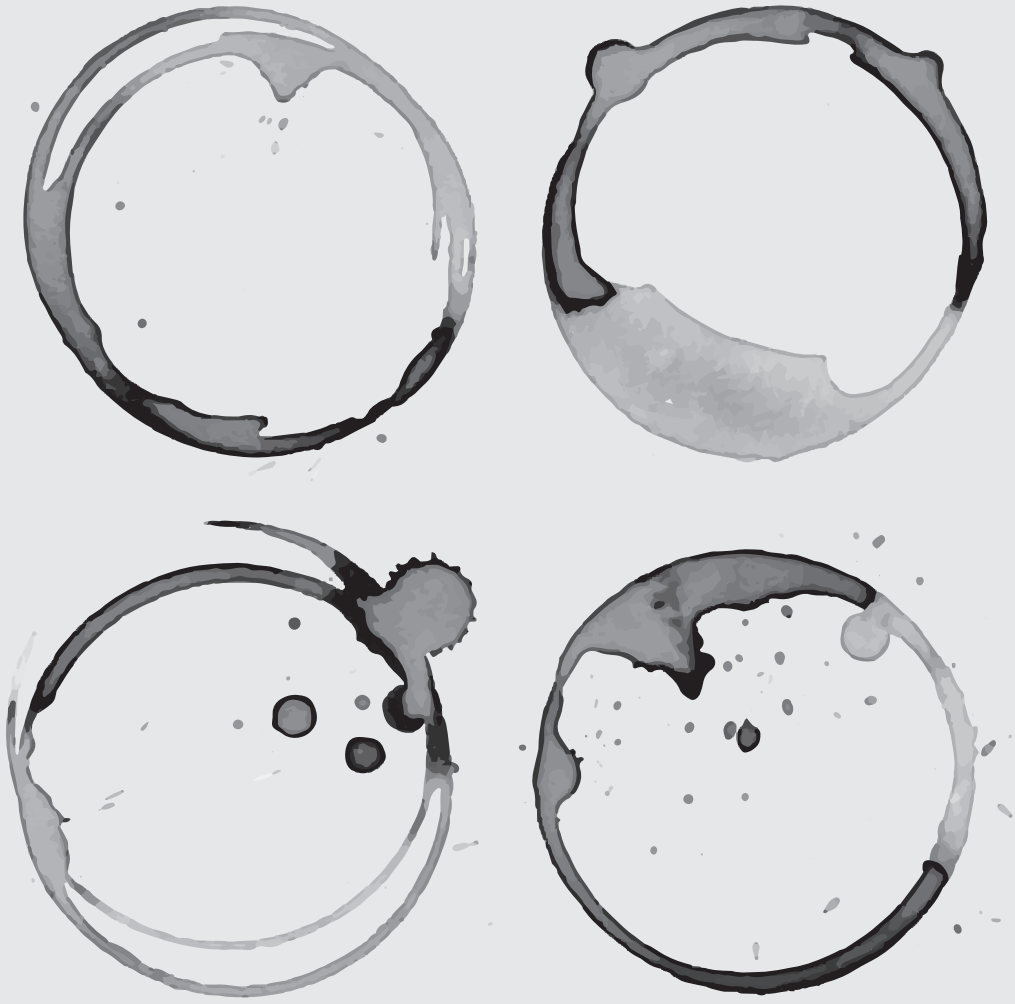

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Psychological profiles after percutaneous coronary intervention:

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Proefschrift

ter verkrijging van de graad van doctor aan Tilburg University op gezag van de rector magnificus, prof. dr. E.H.L. Aarts, in het openbaar te verdedigen ten overstaan van een door het college voor promoties aangewezen commissie in de aula van de Universiteit op vrijdag 18 mei 2018 om 10.00 uur

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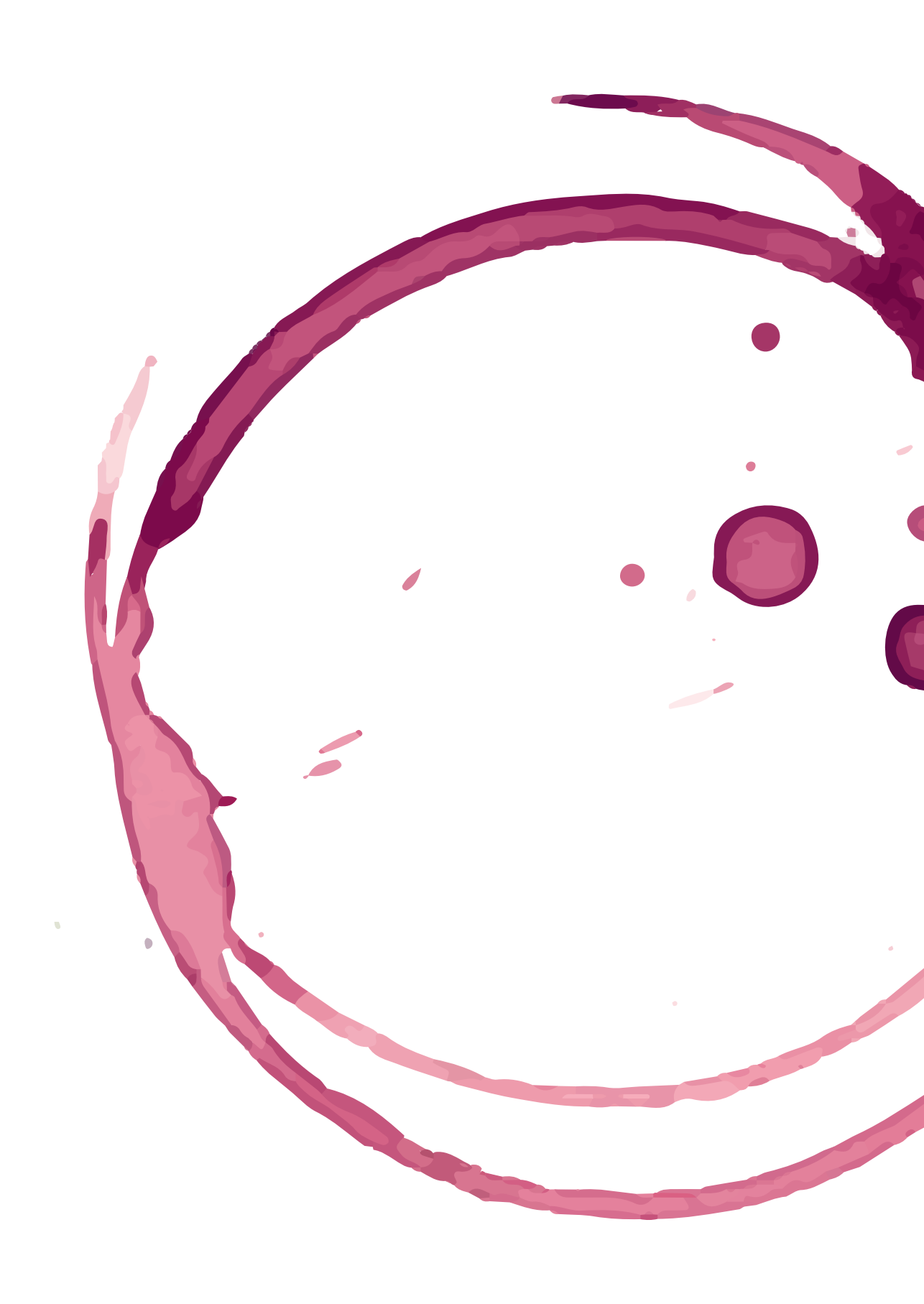
Contents



Chapter 1

General introduction

CORONARY ARTERY DISEASE

Coronary artery disease (CAD) is one of the most common types of cardiovascular disease and accounted for 7.4 million deaths in 2017 in the United Sates (1). In the Netherlands, 450,100 men and 282,100 women suffered from CAD in 2015 (2).

CAD is mainly caused by atherosclerosis, which includes a progressive narrowing of coronary arteries by stenotic occlusions that build up inside of the lumen (3). These occlusions are plaques, resulting from a complex process of build-up of fat, cholesterol, white blood cells, blood platelets, and later on calcium (3). Atherosclerosis may be asymptomatic for years, but when the blood supply to part of the heart muscle becomes limited, it will lead to ischemic chest pain (3). This pain may be chronic or acute, resulting from a sudden rupture of a plaque and formation of a thrombus or blood clot.

PERCUTANEOUS CORONARY INTERVENTION

Percutaneous coronary intervention (PCI) has become a mainstay non-surgical procedure to treat CAD by inserting a balloon and stent into the diseased artery to treat the occlusion (Figure 1, Figure 2) (4). Large randomized controlled trials and population studies have shown the efficacy and benefit of this procedure (4-6). In 2012, 45,305 CAD patients received a PCI in the Netherlands (7). Indications for PCI may be acute, for immediate relief in the case of clinical life-threatening conditions such as acute coronary syndrome, which refers to any group of clinical symptoms compatible with acute myocardial ischemia ranging from ST-

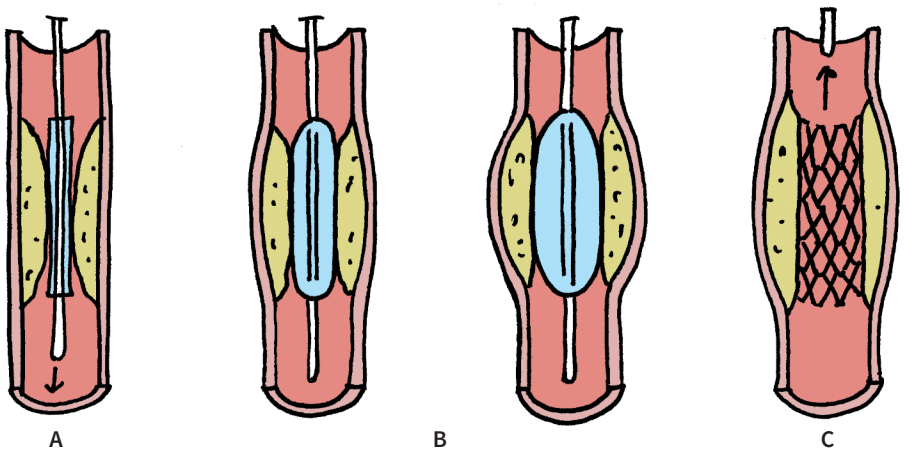


Figure 1. Schematic representation of a PCI procedure.
A. Deflated balloon inserted in the affected artery via a catheter
B. Balloon dilatation
C. Stent placement in the dilated artery
Illustrator: Auke Herrema

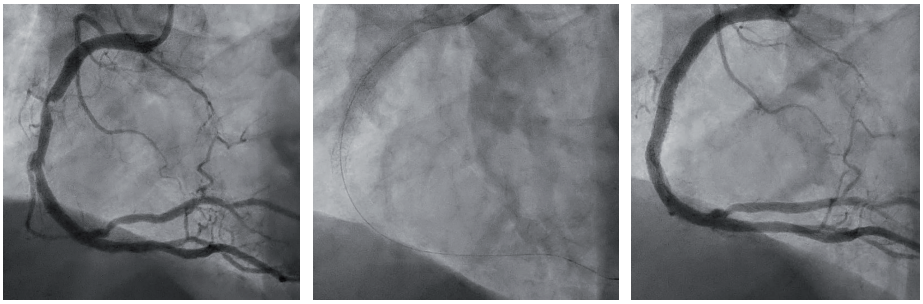


Figure 2. Coronary artery before (left) and after (middle + right) stent placement.

segment elevated myocardial infarction (STEMI), to non ST-segment elevated myocardial infarction (NSTEMI), to unstable angina pectoris (UAP) (8). Elective PCI's are usually scheduled on appointment in stable patients with non-life-threatening considerable stenosis in coronary arteries, and chronic complaints of chest pain (stable angina) (8).

Over the past decades, mortality rates have declined due to improved treatment options, resulting in a longer survival rate of patients with CAD (9). As a consequence of this, CAD has become a long-term chronic condition, putting a high burden on patients, caregivers, and the health care system worldwide (10). Physical (e.g. angina) and psychological symptoms (e.g. depression, anxiety) are common during follow-up and have been shown to decrease patients' well-being (11, 12). After PCI, patients often require long-term treatment and follow-up (13). Treatment regime and lifestyle (e.g. diet, physical activity, smoking, and alcohol use) should be monitored constantly (14). Cardiac rehabilitation is recommended for all PCI patients. Cardiac rehabilitation comprises a fitness, information, psychoeducation and lifestyle component, aiming to optimize lifestyle, treatment adherence, and to relieve potential psychosocial symptoms. Multiple systematic reviews concluded that cardiac rehabilitation in post PCI patients significantly improved health-related quality of life compared with usual care, decreased hospital admissions, and may reduce mortality (15).

HETEROGENEITY IN HEALTH BEHAVIORS AND PATIENT–REPORTED OUTCOMES AFTER PERCUTANEOUS CORONARY INTERVENTION

After percutaneous coronary intervention, there is substantial heterogeneity in patients' health-behavior and in patient-reported outcomes such as physical and psychological symptoms, which may be due to individual differences in demographic, clinical, and psychosocial characteristics. Bandura's social-cognitive theory (Figure 3), which is one of the most comprehensive health behavior models thus far, may give more insight in the

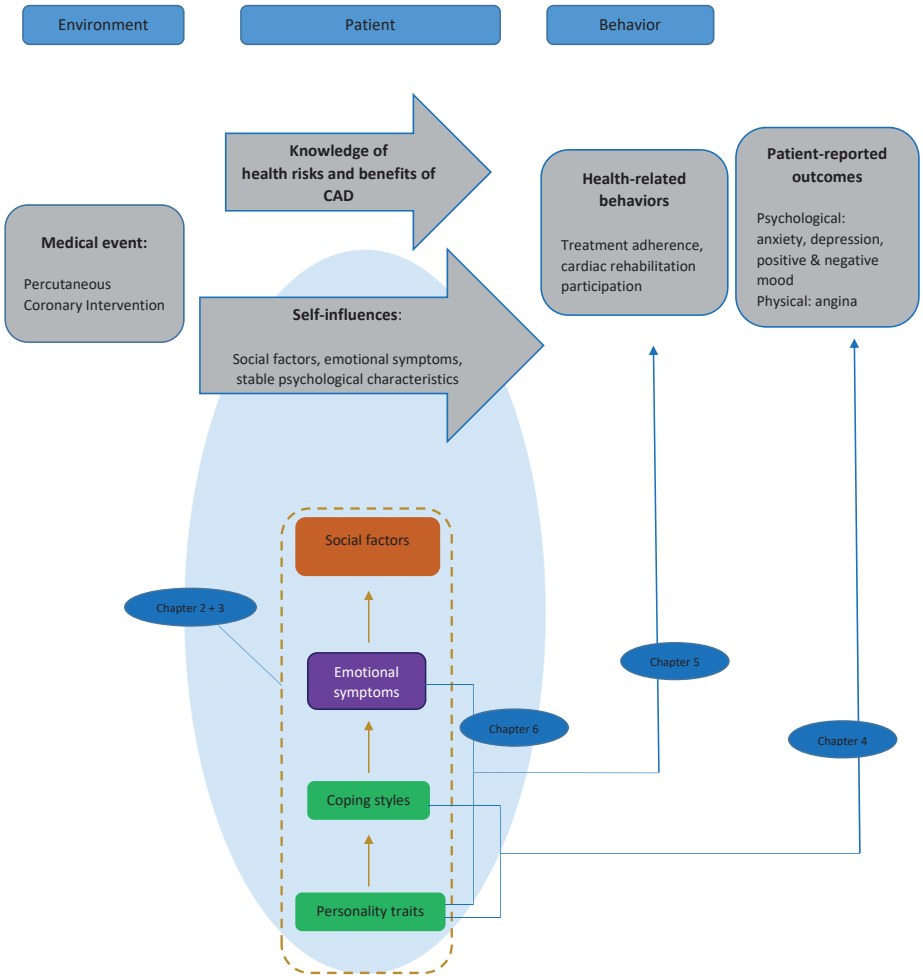


Figure 3. Bandura's social-cognitive theory.

heterogeneity in health behavior and patient-reported outcomes after PCI (16). This model considers patient-reported outcomes as a result of a dynamic interaction between three main constructs: environment, patient, and behavior (16). Interactions between these constructs may occur in various ways.

After PCI, which can be considered an external influence on the patient (environmental variable), both patients' knowledge about CAD (e.g., health risks) and patients' personal characteristics (i.e. 'self-influences') may facilitate or inhibit certain health-related behaviors (e.g., participation to cardiac rehabilitation or treatment adherence) (17). Self-influences that may interfere with PCI patients' health-related behavior include social factors, such as socio-economic status (18), social isolation and social support (19), but also chronic stress

in work and family life (20-22). Emotional symptoms may also play a role. Depression (23, 24), a lack of positive emotions (25), and anxiety (26, 27) may act as barriers to treatment adherence, participation to cardiac rehabilitation, and efforts to improve lifestyle (14), while positive mood (28, 29) may promote these behaviors. Moreover, relatively stable psychological characteristics might affect the propensity to experience lower or higher levels of emotional symptoms or induce certain behaviors (30). For example, patients with a Type D personality (combination of negative affectivity and social inhibition) (31), or with elevated levels of neuroticism (32) or hostility (33), are more vulnerable to experience negative emotions such as anxiety and depression after a cardiac event. Patients scoring high on optimism (29, 34) and resilience report better emotional and physical well-being at follow-up (35, 36). Furthermore, patients' coping styles, which can be defined as relatively permanent, individual-specific ways of facing difficulties in stressful situations, may affect patient-reported outcomes (37). Active coping styles, which are directed at taking actions to remove the stressful situation itself, may induce different behavior than emotion-focused coping styles, that aim to minimize distress that is triggered by the stressful situation (38). On the other side, certain health-related behaviors (e.g. non-participation to cardiac rehabilitation or poor treatment adherence) may affect the patient in various ways (e.g. decreased physical and mental well-being).

Single versus clustered psychosocial factors

In most situations, psychosocial factors do not occur in isolation from one another but tend to cluster in the same individuals and groups. For example, both women and men of lower socio-economic status experiencing high levels of chronic stress are more likely to be depressed, hostile, and socially isolated (39). Importantly, the effects of clusters of psychosocial factors may differ from the effects of single psychosocial factors. For example, it has been shown that the combination of social deprivation, stress at work or in family life and depression is associated with a higher risk for adverse medical events than single factors (40). Above, psychosocial symptoms often co-occur, such as depression and anxiety symptoms (41). However, in Bandura's social-cognitive model, it is still unclear how specific combinations of psychosocial factors induce certain health-behaviors affecting patient-reported outcomes (Figure 3).

Variable–centered versus person–centered approach

To get insight in how specific combinations or clusters of psychosocial factors may explain heterogeneity in patient-reported outcomes of CAD patients, a person-centered perspective is required. This approach, where the unit of analysis is the patient, studies individual

psychosocial patterns or profiles. However, to date most research on psychosocial factors in CAD patients is based on a variable-centered approach, which strives to group similar variables or "traits" together, assuming that the population is homogeneous in how these traits operate on outcomes (42, 43).

A variable-centered approach isolates psychosocial characteristics on which patients reliably differ, and studies their correlational structure, stability over time, and predictive validity for specific outcomes (44). Consequently, this approach is well suited for addressing questions that concern the relative contributions that predictor variables make to a specific outcome (43). However, variable-centered approaches provide no information about the patient-specific intra-individual organization of psychosocial processes and behavior. Instead, variable-centered approaches provide information about the trait structure, stability, and validity for an average person in the sample (44). In addition to its neglect of these intra-individual differences in, the variable-centered approach derives the relevant information from characteristics studied in isolation from each other. Therefore, it misses the key point that different psychological processes, behaviors and traits do not function in isolation from each other within a person but function as a coordinated system of processes, behaviors, and traits (44).

In contrast, a person-centered approach aims to identify groups of individuals who share particular attributes or show similar scoring "profiles" (42, 43), which capture unique patient information that is not well covered by the use of multiple isolated trait scores (44). This approach assumes that the population is heterogeneous with respect to how specific predictors operate on outcomes. Person-centered techniques focus on individual patients and try to understand these patients' behavior from their individual characteristics. Identifying psychosocial profiles might be helpful for a better understanding of the heterogeneity in psychosocial characteristics that may affect patient-reported outcomes in CAD patients, but also for personalized medicine, which aims to individualize care according to the patients' unique characteristics (45-47).

Screening for psychosocial factors

In line with the person-centered approach, several international cardiology workgroups from the European Society of Cardiology (ESC) and the American Heart Association recommend a "*routine screening for CAD patients' psychosocial profile*" (48-50), because earlier and standardized identification of psychosocial risk markers may initiate sooner appropriate personalized care (49). After a short, standardized clinical interview, tailored clinical management by a qualified professional should follow (49, 51). However, there is substantial discussion on the value of screening, as studies examining depression screening have not yet reported improved CAD outcomes (8-12). There are multiple reasons for this, including the level of adequate psychological or psychiatric treatment following a positive screen,

physician awareness and recognition of the psychosocial problems of their patients, as well as the availability of quick, physician-friendly screening instruments (10, 13). Another reason that may explain the inconsistent findings of studies that examined the value of depression screening may be that these studies only included one single factor instead of patients' complete psychosocial profile. Consequently, we considered this discussion an incentive for more in-depth research rather than questioning the usefulness of screening.

In the 2012 guidelines of cardiovascular prevention, the ESC suggested a brief multidimensional psychosocial screening interview that can be used during a physician's clinical contact (49). Its focus is on the seven psychosocial constructs with the most solid evidence for being a risk marker: depression (24) and anxiety (27), perceived stress (22), hostility (33), lower socio-economic status (52), lack of social support (19), and Type D personality (49). However, up to now this instrument has not yet been validated or tested in CAD patients.

OVERALL AIM OF THE DISSERTATION: IDENTIFYING PSYCHOSOCIAL PROFILES

The aim of this dissertation is to explain heterogeneity in patient-reported outcomes of PCI patients, through identifying intra-individual psychological profiles. These multidimensional profiles incorporate transient variables, more stable psychological characteristics, and chronic stress constructs. Both, positive and negative variables are included. This knowledge will expand existing theories focusing on health-related behavior (e.g. treatment adherence and cardiac rehabilitation participation) and patient-reported outcomes (e.g. mental and physical well-being).

Both *Chapter 2* and *Chapter 3* focus on the multidimensional psychosocial screening instrument as proposed by the European Society of Cardiology (ESC). In *Chapter 2*, the psychometric properties of this interview are evaluated. Internal validity of the interview is assessed with a variable-centered factor analysis. To investigate the construct validity, we examine the congruence of its questions with clinically widely used diagnostic instruments. The predictive validity is explored by examining the prospective association of screening scores with angina and cardiopulmonary symptoms 1 year after coronary treatment. In *Chapter 3*, we aim to identify latent multidimensional risk profiles by applying a person-centered approach to the ESC screening instrument. Additionally, we examine whether these profiles are associated with specific sociodemographic, clinical and psychosocial characteristics. In *Chapter 4*, we also aim to determine multidimensional latent psychological profiles by applying a person-centered approach, but this time based on a set of relatively stable psychological individual differences. Additionally, we examine how these profiles were associated with multiple health-behaviors and patient-reported outcomes at follow-up.

Previous studies have mainly focused on individual negative psychological concepts, and knowledge about interrelations between and interactions of multiple negative and positive psychological constructs in the prognosis of PCI patients is still lacking. Therefore, *Chapter 5* reports on interrelations between and independence of multiple positive and negative psychological constructs. Additionally, this chapter investigates whether assessment of positive psychological functioning is of incremental value to the assessment of negative psychological functioning. *Chapter 6* continues the analysis of positive psychological constructs. The course of anxiety and depressive symptoms may be affected by the medical context in which the PCI has been performed. Experiencing a PCI after a life-threatening myocardial infarction (being rushed to the hospital) might, for example, affect patients differently than receiving an elective PCI for ongoing, stable chest pain in the context of CAD. Moreover, an individual's personality might affect the extent and shape of the emotional response as well. It is well known that after trauma, several distinctive response patterns can be observed. Chapter 6 aims to investigate the association of optimism and trait stress resilience with these emotional trauma response profiles in patients who received a PCI either for a life threatening or a non-life threatening situation.

The current study's design, as many of the studies focusing on the association between psychological factors and clinical course in coronary artery disease, may be sensitive for selection-bias. Systematic differences regarding baseline characteristics, exposure to risk factors, or outcome variables between patients who participate, patients who refuse to participate ("non-respondents"), and patients who are lost to follow-up ("drop-outs") may arise when specific patient characteristics (e.g. demographics, disease severity, psychological factors, comorbid diseseas) interfere with patients' motivation for study participation or completion. Therefore, *Chapter 7* focuses on the profiles of participants who completed the study, those who quit participation during follow-up, and those who refused to participate, based on demographic, medical and psychological patient characteristics.

GENERAL RESEARCH DESIGN

The **T**ilburg **H**ealth **O**utcomes **R**egistry of **E**motional **S**tress after **C**oronary **I**ntervention (THORESCI) study is a large, ongoing prospective observational cohort study that started inclusion in December of 2013. All eligible patients receiving a percutaneous coronary intervention (PCI) in the Cardiology clinic of the Elisabeth-TweeSteden hospital in Tilburg are approached for participation to this survey study. THORESCI includes both elective PCI patients (planned intervention when stable coronary artery disease was diagnosed) and acute PCI patients (urgency treatment for acute coronary syndrome in patients diagnosed with either first-time acute coronary syndrome, or already existing coronary artery disease).

To be eligible to participate, patients should be 18 years or older, and have a sufficient understanding of the written and spoken Dutch language. Patients with a life threatening comorbidity (e.g., metastasized cancer) are excluded. On the day of the PCI, the patient receives information about the study content and its requirements by a member of the research team. When participants give written informed consent, they are asked to fill out a set of validated psychosocial questionnaires, spread over five measurement moments post-PCI, i.e., immediately following PCI (0-5 days post-PCI; T0), and at 1 (T1), 6 (T2), 12 (T3) and 24 (T4) months thereafter. For this dissertation, data from T0, T1, T2, and T3 were used. The ESC psychosocial screening interview is conducted at the bedside, within the first hours after the intervention in the elective PCI group, and at 1 month after the intervention by phone (coinciding with the second survey) in the acute PCI group. The study protocol is in keeping with the Helsinki declaration. Written informed consent is obtained from all patients, and the study protocol was approved by the institutional medical ethics review board (METC Brabant). THORESCI is also registered in the clinical trials registration, provided by the U.S. National Library of Medicine.

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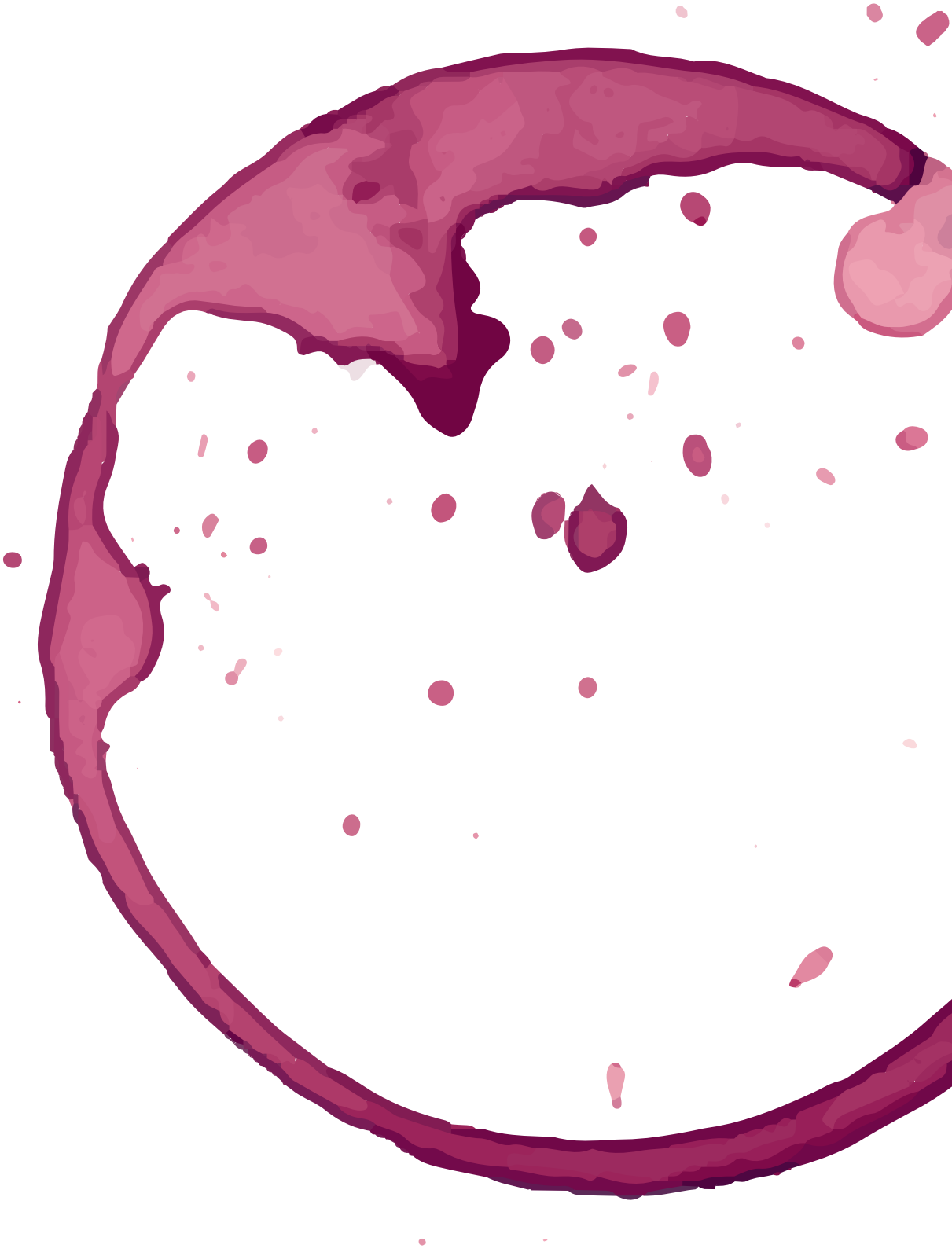

Chapter 2

Validity of the European Society of Cardiology's psychosocial screening interview in patients with coronary artery disease – the THORESCI study

van Montfort E, Denollet J, Widdershoven J, Kupper N

Psychosomatic Medicine 2016; 79:404-415

ABSTRACT

Aim: To examine the validity of the European Society of Cardiology (ESC) psychosocial screening instrument.

Method: 508 acute (67%) or elective (33%) percutaneous coronary intervention (PCI) patients (mean age=63 years, SD=10; 81% male) completed the ESC screening interview and established questionnaires for reputable psychosocial risk markers, i.e., depression (PHQ-9), anxiety (GAD-7), Type D personality (DS14), hostility (CMHS-7), and marital/work stress (MMQ-6, ERI) during or close after hospital admission. At 1-year follow-up angina and cardiopulmonary symptoms were assessed.

Results: Prevalence of psychosocial distress was moderate according to the ESC screener (depression (18%), anxiety (33%), negative affectivity (11%), social inhibition (41%), work stress (17%), marital stress (2%), hostility (38%)). Analysis of correspondence with validated questionnaires revealed fair to moderate agreement (depression (Kappa=.39), anxiety (Kappa=.23), Type D personality (Kappa=.21)), regardless of PCI indication. For work and marital stress, there was poor to fair performance (Kappa range: .04-.24); agreement for hostility was poor (Kappa=-.27). A positive ESC screen for depression, anxious tension and Type D personality was associated with more angina and cardiopulmonary symptoms at follow-up (ORs ranging between 1.85 (95%CI=0.84-4.08) and 8.01 (95%CI=2.35-27.35).

Conclusions: The ESC screener contributes to the search for a multidimensional and easy-to-use psychosocial screening instrument for cardiac patients. Although the screener, in its current form, may not be sufficiently valid to reliably detect all predefined psychosocial factors, screening scores for depression and anxiety might be useful in clinical practice. Our findings can be used for the further refinement and validation of the screener.

INTRODUCTION

Accumulating evidence suggests that different psychosocial factors are associated with cardiovascular disease (CVD). These include depression (1), anxiety (2), perceived stress (3), hostility (4), lower socio-economic status (5), lack of social support (6), and Type D personality (7). Psychosocial factors may have a negative influence on the incidence and course of multiple cardiovascular conditions (8-11), including coronary heart disease, ventricular tachyarrhythmia, and sudden cardiac death, and may act through several distinct psychobiological mechanisms that are directly involved in the pathophysiology of CVD (11). These psychosocial factors may also act as a barrier to treatment adherence and efforts to improve life-style behaviors (12, 13). In addition, patients with elevated psychosocial risk markers demonstrate worse patient reported outcomes (e.g., decreased wellbeing and health-related quality of life) and may experience more symptoms and more percutaneous coronary intervention (PCI)-related complications (14, 15). Finally, suffering from CVD and undergoing its treatment may lead to (more) psychosocial problems (15), like stress (16), depression, and even posttraumatic stress disorder (17).

To relieve suffering and enhance health-related quality of life, and coronary heart disease prognosis, it may be helpful to know a patient's personal psychosocial risk profile (14, 18). Earlier and standardized identification of psychosocial risk markers may initiate appropriate care sooner (14). Therefore, several international cardiology workgroups from the European Society of Cardiology (ESC) and the American Heart Association recommend a "*routine screening for psychosocial factors*" in patients with coronary heart disease (14, 18-20). However, psychosocial screening is only meaningful when required psychological care supports are in place to assure accurate diagnosis, effective treatment and follow-up by a qualified professional (20, 21).

Nevertheless, there is substantial discussion on the value of screening, as studies examining depression screening have not yet reported improved CVD outcomes (22-26). There may be multiple reasons for this, including the level of adequate psychological or psychiatric treatment following a positive screen, physician awareness and recognition of the psychosocial problems of their patients, the patient's willingness to disclose problems, as well as the availability of quick, physician-friendly screening instruments (21, 24). This discussion should be an incentive for more in-depth research rather than questioning the usefulness of screening.

To date, there is no validated instrument or protocol that systematically screens a range of psychosocial risk factors in cardiac patients. Standardized measurements for individual psychosocial factors are available in many languages and countries (27-31). In their guidelines of 2012, the ESC suggests a brief psychosocial screening interview that can be used during a physician's clinical contact (14). Its focus is on the seven constructs

with the most solid evidence for being a risk marker: depression (1), anxiety (2), perceived stress (3), hostility (4), lower socio-economic status (5), lack of social support (6), and Type D personality (14). However, the ESC psychosocial screening instrument has not yet been validated or tested. Therefore, the aim of the current study was to evaluate the psychometric properties of the ESC psychosocial screening instrument in a real-world cardiac patient population. To investigate the construct validity of the screening instrument, we examined the congruence of its questions with clinically widely used (diagnostic) instruments in patients undergoing PCI. The predictive validity was explored by examining the prospective association of the screening scores with angina and cardiopulmonary symptoms one year after coronary treatment.

METHODS

Patient population and procedure – THORESCI study

The **T**ilburg **H**ealth **O**utcomes **R**egistry of **E**motional **S**tress after **C**oronary **I**ntervention (THORESCI) study is a large, prospective observational cohort study that started inclusion in December of 2013. All eligible patients receiving a PCI in the Cardiology clinic of the Elisabeth-TweeSteden hospital in Tilburg were approached for participation to this prospective survey study. The sample included both elective PCI patients (planned intervention when stable coronary artery disease was diagnosed) and acute PCI patients (urgency treatment for acute coronary syndrome in patients diagnosed with either first-time acute coronary syndrome, or already existing coronary artery disease). To be eligible to participate, patients should be 18 years or older, and have a sufficient understanding of the written and spoken Dutch language. Patients with a life threatening comorbidity (e.g., metastasized cancer) were excluded. On the day of the PCI, the patient received information about the study content and its requirements by a member of the research team. When participants gave written informed consent, they were asked to fill out a set of validated psychosocial questionnaires, spread over five measurement moments post-PCI, i.e., immediately following PCI (0-5 days post-PCI), and at 1, 6, 12 and 24 months thereafter. The ESC psychosocial screening interview was conducted at the bedside, within the first hours after the intervention in the elective PCI group, and at 1 month after the intervention by phone (coinciding with the second survey) in the acute PCI group. The study protocol is in keeping with the Helsinki declaration. Written informed consent was obtained from all patients, and the study protocol was approved by the institutional medical ethics review board (METC Brabant).

The ESC Psychosocial Screening Instrument

All patients underwent the ESC psychosocial screening interview, which is a 15-item, 5 minute interview put forward by the ESC as a quick assessment of psychosocial problems during medical consultation (14). Three of the predefined components are tapping into social factors, such as perceived marital or financial stress, socio-economic status and social isolation. The other four components assess depression, anxiety, hostility, and Type D personality. To develop this screening instrument, the ESC consulted an expert panel (personal communication NK with one of the guideline authors (C. Albus)). Briefly, for work stress, hostility, and Type D composite questions were formulated, capturing the essence of the construct, for depression and anxiety the PHQ-4 was used (32). All 15 questions are rated with "yes" or "no" by the interviewer, with the exception of the educational degree question, which has four response categories. For the present study, these questions were translated into Dutch, using the translation-back translation method. In the ESC guidelines, no cut-off score is defined, but it is suggested that no more than mandatory education and/or a "yes" for one or more items can be considered as an indication to discuss the relevance of psychosocial factors with respect to quality of life and medical outcome, and subsequently further tailored clinical management (14).

Validation scales

Depression - The Patient Health Questionnaire (PHQ-9) was used to assess symptoms of depression (29). This self-administered version of the primary care evaluation of mental disorders (PRIME-MD) has comparable diagnostic validity for depression as the clinician-administered PRIME-MD (33). The items cover the nine DSM-IV diagnostic criteria for depressive disorder, making it a self-report instrument that can establish a provisional depression diagnosis (33). Items are rated on a Likert scale from 0 ("not at all") to 3 ("almost every day") (29). We used the recommended cut-off score ≥10 to screen for depression (both sensitivity and specificity 88% as compared to clinical diagnosis) (29). Cronbach alpha of the PHQ-9 was .84 in this study.

Anxiety - Symptoms of generalized anxiety were measured with the 7-item Generalized Anxiety Disorder (GAD-7) scale (30). The GAD-7 items are scored on a Likert scale from 0 ("not at all") to 3 ("almost every day") (30). We used the recommended cut-off score ≥10 to assess anxiety (sensitivity is 89% and specificity 82% in comparison with a clinical diagnosis) (30). Cronbach alpha of the GAD-7 was .91 in the current study.

Type D personality - Type D personality was assessed with the 14-item Type D scale (DS14) that comprises two 7-item subscales, negative affectivity (e.g., "I am often in a bad mood) and social inhibition (e.g., "I often feel inhibited in social interactions) (34). All items

are rated on a five-point Likert scale from 0 ("false") to 4 ("true"). We used a standardized cut-off score ≥10 on both subscales to identify Type D personality (34, 35). Cronbach alpha was .88 for Negative Affectivity and .90 for Social Inhibition in this study.

Work stress – Effort/reward balance was determined using the Dutch 16-item version of the Effort Reward Imbalance scale (36); e.g. "I have constant time pressure due to a heavy work load". All items are rated on a four-point Likert scale from 1 ("strongly disagree") to 4 ("strongly agree"). We used the upper quartile as a cut-off to indicate disrupted effort/reward balance. Cronbach alpha was .90 in the current study. Further, the Work Ability Index (37) was administered one year after the PCI. For the current analyses only the question "Did you experience much stress during your work?" from the section "work situation before your illness (i.e. heart incident)" was used. Patients had to answer this question with "yes"/"no". A positive response on this question served as an indication for high work stress prior to PCI.

Marital stress – Marital quality was determined using a six-item version of the Maudsley Marital Questionnaire (MMQ) (38). All items (e.g. "Can you let your partner know your true feelings?") are rated on a 7-point Likert scale from 0 (e.g., "Frank and open with partner") to 6 (e.g., "Conceal all the emotions all the time"). Total scores can range from 0 to 36 with higher scores indicating less marital quality. We used the upper quartile as a cut-off to determine low marital quality. Cronbach alpha of the MMQ-6 was .98.

Hostility – The 7-item "Williams" subscale of the Cook-Medley Hostility Scale (CMHS-7) was used to assess cynicism, hostile attribution and affect, and aggressive responding (39). This subscale was chosen because of its prognostic performance regarding adverse cardiovascular outcomes (40). All items (e.g., "I have often had to take orders from someone who did not know as much as I did.") are answered with true/false. Hostility was added later to the study, at one year after PCI. We used the upper quartile as a cut-off to indicate high hostility. Cronbach alpha of the CMHS-7 was .69 in this study.

Cardiopulmonary symptoms and angina one year after PCI

Cardiopulmonary symptoms – Cardiopulmonary problems (e.g., shortness of breath, chest pain, tightness of the chest) were determined one year after PCI using the Cardiopulmonary symptoms subscale of the Health Complaints Scale (41). Patients rated to what extent they experienced six cardiopulmonary problems during the recent past on a five-point Likert scale from 0 ("not at all") to 4 ("a lot"). This scale is valid and reliable (41).

Angina– Angina symptoms were assessed one year after PCI with the Seattle Angina Questionnaire (SAQ-7) (42), which is a disease specific self-report measure for patients with coronary artery disease. Scores range from 0 to 100. The SAQ-7 is a valid measure (42) and Cronbach alpha in the present study was .82.

Demographic and clinical variables

Demographic variables were obtained from self-report questionnaires and patients' medical records, both at baseline and 1-month post PCI. Demographic variables included sex, age, and educational level. Educational level was recoded into two categories: low vs. higher education (at least high school) for presentation purposes. Clinical variables, i.e. diagnosis, indication for PCI procedure (elective vs. acute (i.e., acute coronary syndrome (ST Segment Elevation Myocardial Infarction (STEMI), nonSTEMI and unstable angina)), cardiac disease history and risk factors (family history, hypercholesterolemia, diabetes mellitus type 2) were extracted from the patients' medical records.

Statistical analyses

To determine the latent structure of the 15-item ESC screening instrument, exploratory factor analysis, with principal axis factoring and Oblimin rotations, was used. This is a method to condense the 15 items down to a smaller, more manageable number of dimensions or factors (43). Catell's scree test and Eigenvalues (>1.0) (43) were explored to determine the number of factors. To assign items to a factor, we considered the items' factor loading in the rotated factor solution (>.45), together with the theoretical fit of the item within the factor.

Next, the relationships between scores on the ESC screening instrument and scores on the widely used and validated questionnaires were examined. We calculated cross tables using the dichotomized scores on the validation instruments and calculated Cohen's Kappa as a measure of agreement between questionnaires (44). The cross tables were used to compare the frequency of patients reporting psychosocial symptoms according to the ESC screener with the number of patients having significant psychosocial symptoms according to the existing questionnaires. For all risk markers, we calculated sensitivity (i.e. ability of the ESC screener to correctly classify an individual as having psychosocial distress compared to the validation instrument), specificity (i.e. ability of the ESC screener to correctly classify an individual as not having psychosocial distress compared to the validation instrument), positive predictive value (PPV; i.e. percentage of participants with a positive ESC screening score who also have a positive score on the validation instrument) and negative predictive value (NPV; i.e. percentage of participants with a negative ESC screening score who also have a negative score on the validation instrument).

Whereas the ESC Screening Instrument guidelines (14) suggest that no more than mandatory education and/or a "yes" for one or more items can be considered as an indication for further research of a patient's psychological functioning, validity of an alternative scoring profile adhering to the PHQ-2 and GAD-2 guidelines was also examined (i.e. "yes" to both depression/anxiety items) (45, 46).

Finally, logistic regression analyses were conducted to explore the predictive value of scores on the ESC screening instrument and 1-year outcomes (i.e. angina and cardiopulmonary symptoms). Previous work showed that psychological (e.g. worry) and somatic symptoms (e.g. tension) of anxiety may contribute through different psychobiological mechanisms to the pathophysiology of CVD (11). Therefore, predictive validity for the two anxiety ESC screening items was studied separately. Additionally, linear regression analysis with continuous dependent variables were performed. All statistical analyses were performed using SPSS 22 (IBM SPSS Statistics for Windows, Version 22. Armonk, NY: IBM Corp USA).

RESULTS

Sample characteristics

Of the 817 eligible patients who were approached for participation between December 2013 and July 2015, 163 (20%) refused participation to the study. In August 2015, data extraction from this ongoing cohort resulted in a sample of 508 patients with ESC screening (81% male, mean age=63±10; 95% Caucasian). Baseline characteristics are presented in Table 1; 72% of this sample completed both the ESC screening and PHQ-9/GAD-7 questionnaires within one month after PCI, and 70% completed the DS14. There were various reasons for these missing questionnaire data. In the acute PCI group, some participants who completed the

Table 1. Baseline Patient Characteristics (n=508)

	N	%
Demographics		
Sex (men)	407	81
Age	63 (SD=10)	-
Lower education[a] (≤ 8years)	148	29
Currently employed[b]	187	40
Medical		
Cardiac history [c,1]	354	75
Risk factors		
Family history of CVD< 60 years[e]	200	42
Hypercholesterolemia[e]	186	39
Diabetes Mellitus Type 2[b]	60	12
PCI indication[b]		
Acute	333	67
Elective	164	33

CVD = Cardiovascular Disease, PCI = percutaneous coronary intervention; Missing values: [a]3 (1%), [b]11(2%), [c]42 (8%), [d]35 (7%), [1]previous myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, angina pectoris and/or atrial fibrillation.

ESC screening failed to fill out the standard questionnaires within one month post-PCI, and only completed these measures at follow-up. Other patients dropped out of the study soon after returning from the hospital. Angina and other cardiopulmonary symptoms were assessed in patients with 1-year follow-up (n=201).

Factor Analysis

The 15 items of the ESC screening interview were subjected to principal component analysis. First, the suitability of the data for factor analysis was assessed. Inspection of the correlation matrix revealed the presence of many coefficients of .25 and above. The Kaiser-Meyer-Olkin value was .7, exceeding the recommended value of .6 and the Barlett's Test of Sphericity (47, 48) reached statistical significance, supporting the factorability of the correlation matrix. Factor analysis revealed the presence of five components with eigenvalues exceeding 1 (Table 2) and the scree plot (49) also showed a clear break (elbow) after the fifth component (Figure 1). Only components above this point were retained, leaving five components for further investigation. The five-factor solution explained 53.3% of the variance.

Oblimin rotation was performed to aid in the interpretation of these five components, resulting in five components with strong loadings and almost all variables loading substantially on only one component, except for one item on *Family stress*. In addition, some moderate cross-loadings were observed (Table 2).

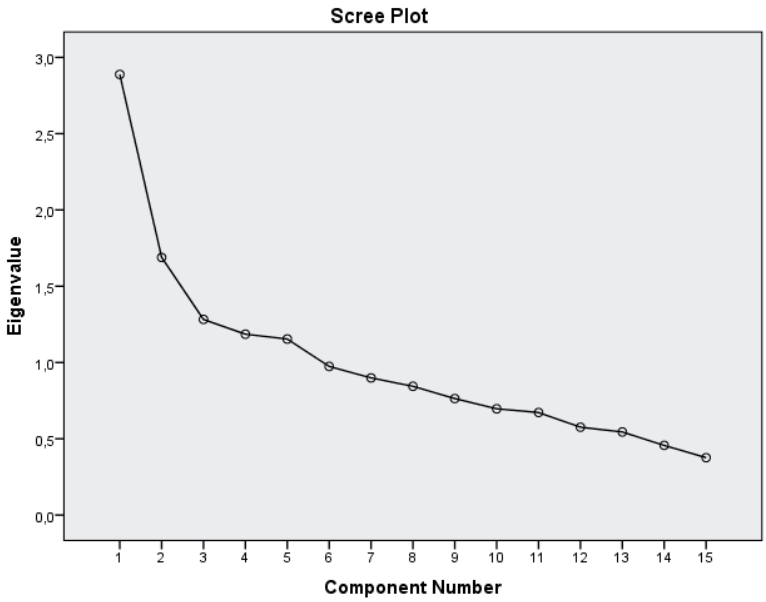

Figure 1. Scree plot for exploratory factor analysis on the items of the European Society of Cardiology's psychosocial screening interview.

Table 2. Structure Coefficients of the ESC Screening Instrument (n=508)

		Components Factor Analysis				
Predefined Components	Items ESC Screening Instrument	Emotional Distress	Work	Hostility	Social Resources	Social Stress
Depression	down, depressed, and hopeless	.80	.01	-.08	-.03	.09
Type D (NA)	often anxious, irritable, or depressed	.77	.11	-.17	.06	.15
Anxiety	feeling anxious, nervous, on edge	.63	.17	-.28	.29	-.03
Depression	lost interest and pleasure	.60	-.05	-.13	-.08	.30
Anxiety	unable to stop or control worrying	.49	.25	-.24	.13	.28
Work stress	lack control over demands at work	.03	.77	-.11	-.19	.12
Work stress	reward inappropriate for effort	.23	.73	-.08	.02	.06
Low SES	manual worker	-.07	.71	-.09	.08	-.02
Hostility	annoyed about other people's habits	.09	.10	-.85	-.02	.10
Hostility	angry over little things	.27	.10	-.78	.01	.06
Low SES	highest educational degree	-.01	.01	-.14	.70	.05
Social isolation	living alone	.23	.01	.07	.54	.14
Family stress	serious problems with spouse	.22	.19	-.30	-.47	.43
Social isolation	lack of close confidant	.17	.04	.01	-.10	.75
Type D (SI)	avoid sharing thoughts and feelings	.10	.06	-.16	.28	.64
Eigenvalues		2.8	1.7	1.2	1.2	1.1
% of variance explained by the component		18	11	8	8	7

ESC = European Society of Cardiology, NA = Negative affectivity, SES = Socio Economic Status, SI = Social Inhibition; ■ loadings >.45.

A first component represents *Emotional Distress*, involving the Negative Affectivity item, both depression items and both anxiety items. Component 2, *Work stress*, involves both work stress questions and the low socio-economic status (SES) item "Are you a manual worker?". A third component covers the *Hostility* items. Fourth, the items "highest educational degree", "living alone" and "relationship problems" cluster together in a *Social Resources* component. This "relationship problem" item is also loading on the fifth component (*Social Stress*), further comprising "having a close confidant" and the social inhibition item. Some cross-loadings were observed, e.g. for "lost interest and pleasure", which also partly loaded on the *Social Stress* component, or the "marital stress item" which loaded on multiple factors (Table 2).

Concordance with validated instruments for Depression, Anxiety and Type D personality

From the 508 participants who completed the ESC interview, 90 (18%) patients reported a positive screen for one or both depression items of the ESC psychosocial screener. For anxiety, 164 (33%) patients responded positively to one or both items. 24 (5%) patients scored positive on both depression items and 48 (10%) patients reported a "yes" for both anxiety items. The percentage of positive screens were equal for elective and acute patients. The percentages of positive screens for depression and anxiety ("yes" to both items) were higher in women (8% and 12% resp.) than in men (4% and 9% resp.). Fifty-three (11%) patients reported a positive screen on the Negative Affectivity item and 205 (41%) responded positively to the Social Inhibition item. Thirty-one (6%) patients scored positive on both Type D items. According to the self-report validation questionnaires (PHQ-9, GAD-7, DS14), 12% crossed the threshold for at least moderate clinical depression, 8% reported at least moderate levels of clinical anxiety, 30% reported the presence of Negative Affectivity and 36% the presence of Social Inhibition. Table 3 presents scores on the individual items of the screening interview and the percentages of patients who scored above the cut-off on the linked validation questionnaires.

Depression & anxiety

"Yes" to at least one ESC screening item - Cohen's Kappa statistic indicated fair to moderate agreement [κ=.39] between the ESC screener and the PHQ-9. Cross tables showed moderate sensitivity, but high specificity when compared to the PHQ-9 (Table 4). For anxiety, there was only fair agreement [κ=.23] between the ESC anxiety items and the GAD-7. Both sensitivity and specificity were moderate to high (Table 4). Both for depression and anxiety, the positive predictive value was relatively low (Table 4).

"Yes" to both ESC screening items – Using this more stringent criterion, Cohen's Kappa tests for agreement between measures showed better agreement between the ESC screener and the full instruments, with κ being .43 (moderate) for depression and .38 (fair to moderate)

Table 3. Components of the ESC Psychosocial Screening Instrument linked to validation questionnaires (n=508)[a]

Predefined Components	Items ESC Screening Instrument	Positive scores ESC Screening	Positive scores Validation questionnaires
Low SES	1. What is your highest educational degree?		
	University, higher education, or equal	129 (26%)	
	Secondary education or equal	228 (45%)	
	Further education or equal	94 (19%)	
	Primary school (or less)	54 (11%)	
	2. Are you a manual worker?	104 (21%)	
Work/Family stress	3. Do you lack control over how to meet the demands at work?	55 (11%)	**ERI****, (n= 217): 55 (25%);
	4. Is your reward inappropriate for your effort?	57 (11%)	**Work stress**, (n= 210): 85 (41%)
	5. Do you have serious problems with your spouse?	12 (2%)	**MMQ-6****, (n= 320): 90 (28%)
Social isolation	6. Are you living alone?	107 (21%)	
	7. Do you lack a close confidant?	475 (94%)	
Depression (PHQ-2)	8. Do you feel down, depressed, and hopeless?	73 (15%)	**PHQ-9***, (n=366): 42 (12%)
	9. Have you lost interest and pleasure in life?	42 (8%)	
Anxiety (GAD-2)	10. Do you frequently feel nervous, anxious, or on edge?	113 (22%)	**GAD-7***, (n=369): 31 (8%)
	11. Are you frequently unable to stop or control worrying?	99 (20%)	
Hostility	12. Do you frequently feel angry over little things?	126 (25%)	**CMHS-7****, (n=83): 34 (41%)
	13. Do you often feel annoyed about other people's habits?	135 (27%)	
Type D personality	14. In general, do you often feel anxious, irritable, or depressed?	53 (11%)	**DS14*** (NA: n=359): 106 (30%) (SI: n=356); 128 (36%)
	15. Do you avoid sharing your thoughts and feelings with other people?	205 (41%)	

ESC = European Society of Cardiology, SES = Socio-Economic Status, ERI = Effort Reward Imbalance scale, MMQ-6 = Maudsley Marital Questionnaire-6, PHQ-9 = Patient Health Questionnaire-9, GAD-7 = Generalized Anxiety Questionnaire-7, CMHS-7 = Cook Medley Hostility Scale-7, DS14 = Type D Scale-14, NA = Negative Affectivity, SI = Social Inhibition; [a]missing values for all ESC items are <1%; *cut off = 10, **cut off = upper quartile.

for anxiety. This resulted in an increase in specificity but a decrease in sensitivity (Table 4). The positive predictive value was much higher, at 70% for depression and 43% for anxiety.

Concordance percentages for depression and anxiety were comparable in both PCI groups (elective vs. acute patients; see Table 4). With respect to sex differences, comparable results were found in men and women (see supplementary Table).

Type D personality

Negative affectivity & Social Inhibition - Cohen's Kappa statistic indicated fair agreement [NA: κ=.27; SI κ=.20] between the ESC screener and the DS14. For NA cross tables showed poor sensitivity and high specificity, while the positive predictive value was moderate to high (Table 4). For SI sensitivity was low to moderate, specificity was high, and the positive predictive value was low to moderate (Table 4).

Type D personality – Combining the two scales (NA and SI) and comparing this score to the dichotomous Type D assessment on the DS14, the results showed fair agreement between the ESC screener and the DS14 [κ=.21]. Sensitivity was low and specificity was high, while a moderate positive predictive value was observed (Table 4). Concordance percentages were comparable in both PCI groups (elective vs. acute patients; see Table 4), and comparable results were found in men and women (see supplementary Table).

Work stress & Marital stress

Effort-reward imbalance - Cohen's Kappa showed only slight agreement between the ESC effort/reward item and the full questionnaire [κ=.04]. Specificity was high (Table 4). Nevertheless, there were a large number of false negatives, leading to poor sensitivity. Positive predictive value was low.

Lack of control over demands - Cohen's Kappa showed fair agreement between the ESC item and the questionnaire [κ=.24]. Sensitivity was low, while specificity was high (Table 4). The positive predictive value was high, indicating that 84% of patients who reported lack of control over demands on the ESC screener item also reported to have experienced much work stress prior to the PCI on the Work Ability Index item.

Marital stress - Cohen's Kappa showed slight agreement between the ESC effort/reward item and the full questionnaire [κ=.10]. Comparing the ESC martial stress question to the MMQ-6, high specificity and low sensitivity were found (Table 4). The positive predictive value was high.

Hostility

"Yes" to at least one hostility items – Cohen's Kappa indicated no agreement between the ESC screener and the CMHS [κ=-.27]. Results showed low sensitivity, moderate specificity and low positive predictive value.

"Yes" to both hostility questions – Using a more stringent criterion, Cohen's Kappa statistic still indicated a relative disagreement between the ESC screener and the CMHS [κ=-.11]. While specificity was somewhat higher, sensitivity and positive predictive value remained low.

Table 4. Analysis of cross tables of ESC screening scores vs. validation instruments

Depression, n=364*						
ESC Screening instrument	“yes” to at least 1 depression item		PHQ-9		Sensitivity	Specificity
			no	yes	.60	.88
		no	286 (95%)	16 (5%)	PPV	NPV
		yes	38 (61%)	24 (39%)	.39	.05
	“yes” to both depression items		PHQ-9		Sensitivity	Specificity
			no	yes	.35	.98
		no	318 (92%)	26 (8%)	PPV	NPV
		yes	6 (30%)	14 (70%)	.70	.08
			PHQ-9 in elective patients		PHQ-9 in acute patients	
			no	yes	no	yes
		no	103 (92%)	9 (8%)	215 (93%)	17 (7%)
		yes	2 (29%)	5 (71%)	4 (31%)	9 (69%)
Anxiety, n=366*						
ESC Screening instrument	“yes” to at least 1 anxiety item		GAD-7		Sensitivity	Specificity
			no	yes	.73	.76
		no	254 (97%)	8 (3%)	PPV	NPV
		yes	82 (79%)	22 (21%)	.21	.03
	“yes” to both anxiety items		GAD-7		Sensitivity	Specificity
			no	yes	.43	.95
		no	319 (95%)	17 (5%)	PPV	NPV
		yes	17 (57%)	13 (43%)	.43	.05
			GAD-7 elective in patients		GAD-7 in acute patients	
			no	yes	no	yes
		no	102 (94%)	7 (7%)	217 (96%)	10 (4%)
		yes	6 (55%)	5 (46%)	11 (58%)	8 (42%)

Table 4. ***Continued***

Negative Affectivity (NA), n=357*						
			DS14 - NA		Sensitivity	Specificity
			no	yes	.26	.96
	“yes” to NA item	no	241 (76%)	78 (25%)	PPV	NPV
		yes	10 (26%)	28 (74%)	.74	.25
ESC Screening instrument			DS14-NA in elective patients		DS14-NA in acute patients	
			no	yes	no	yes
	“yes” to NA item	no	76 (71%)	31 (29%)	165 (78%)	47 (22%)
		yes	3 (27%)	8 (73%)	7 (26%)	20 (74%)
Social Inhibition (SI), n=353*						
			DS14 - SI		Sensitivity	Specificity
			no	yes	.54	.74
	“yes” to SI item	no	150 (72%)	58 (28%)	PPV	NPV
		yes	76 (52%)	69 (48%)	.48	.28
ESC Screening instrument			DS14 SI - elective patients		DS14 SI - acute patients	
			no	yes	no	Yes
	“yes” to SI item	no	106 (75%)	35 (25%)	44 (66%)	23 (34%)
		yes	47 (50%)	48 (50%)	29 (58%)	21 (42%)

Table 4 continues on next page

Table 4. ***Continued***

Type D, n=353*						
ESC Screening instrument	“yes” to NA and SI		DS14 - Type D		Sensitivity	Specificity
			no	yes	.18	.97
		no	285 (85%)	49 (14%)	PPV	NPV
		yes	8 (42%)	11 (58%)	.58	.85
			DS14 Type D - elective patients		DS14 Type D - acute patients	
	“yes” to NA and SI		no	yes	no	yes
		no	194 (87%)	28 (13%)	91 (81%)	21 (19%)
		yes	6 (43%)	8 (57%)	2 (40%)	3 (60%)
Work stress						
ESC Screening instrument	Disrupted effort/reward balance, n=174*		ERI		Sensitivity	Specificity
			no	yes	.19	.85
		no	137 (76%)	44 (24%)	PPV	NPV
		yes	24 (71%)	10 (29%)	.29	.24
	Lack control over demands item, n=215*		Work stress		Sensitivity	Specificity
			no	yes	.24	.98
		no	103 (67%)	52 (34%)	PPV	NPV
		yes	3 (16%)	16 (84%)	.84	.34

Table 4. ***Continued***

Marital stress, n=320						
ESC Screening instrument	"yes" to spouse problems item		MMQ-6		Sensitivity	Specificity
			no	yes	.08	1.00
		no	229 (74%)	83 (27%)	PPV	NPV
		yes	1 (12%)	7 (88%)	.88	.27
Hostility, n=83						
ESC Screening instrument	"yes" to at least 1 hostility item		CMHS-7		Sensitivity	Specificity
			no	yes	.26	.51
		no	25 (50%)	25 (50%)	PPV	NPV
		yes	24 (72%)	9 (27%)	.27	.50
	"yes" to both hostility items		CMHS-7		Sensitivity	Specificity
			no	yes	.09	.82
		no	40 (56%)	31 (29%)	PPV	NPV
		yes	9 (75%)	3 (25%)	.25	.29

ESC = European Society of Cardiology, PHQ-9 = Patient Health Questionnaire-9, GAD-7 = Generalized Anxiety Questionnaire-7, CMHS-7 = Cook Medley Hostility Scale-7, DS14 = Type D Scale-14, NA = Negative Affectivity, SI = Social Inhibition, ERI = Effort Reward Imbalance scale, MMQ-6 = Maudsley Marital Questionnaire-6, CMHS-7 = Cook Medley Hostility Scale-7, PPV = positive predictive value, NPV = negative predictive, *numbers may differ slightly from those in table 3 due to missing values on either the ESC screener or validation questionnaires.

Predictive validity: Angina and Cardiopulmonary symptoms one year after PCI

We examined the predictive validity of a positive screen for depression (depressed mood and/or anhedonia), anxiety (tension and worry) and Type D personality (Negative Affectivity and Social Inhibition) with respect to significant angina and cardiopulmonary symptoms at 1-year follow-up.

Angina – Univariate logistic regression analysis showed that participants with positive screens on depression, anxious tension and Type D personality had significantly more angina symptoms one year after PCI than participants with a negative screen (see Table 5). There was no relation between anxious worry and one-year angina. Linear regression analysis with continuous dependent variables showed similar results (data not shown).

Cardiopulmonary symptoms - Univariate logistic regression analysis showed that participants with positive screens for depression, anxious tension and Type D personality had significantly more cardiopulmonary symptoms one year after PCI than participants with a negative screen (see Table 5). There was no relation between anxious worry and one-year cardiopulmonary symptoms. Linear regression analysis with continuous dependent variables rendered similar results (data not shown).

Table 5. Results from logistic regression analyses: ESC screening scores and one-year angina and cardiopulmonary symptoms

	Logistic regression analyses					
	Angina			Cardiopulmonary symptoms		
Items ESC Screening instrument	OR	95% CI	p	OR	95% CI	p
Depression[1]	2.38	1.02-5.55	**.045**	2.94	1.27-6.77	**.012**
Anxiety: tension	3.28	1.47-7.35	**.004**	5.56	2.43-12.73	**.000**
Anxiety: worry	1.85	.84-4.08	.127	2.04	.92-4.53	.079
Type D[2]	8.01	2.35-27.35	**.001**	4.26	1.36-13.38	**.013**

ESC = European Society of Cardiology, [1]depressed mood and/or anhedonia, [2]Negative Affectivity and Social Inhibition.

DISCUSSION

The aim of the current study was to, for the first time, test the validity of the proposed ESC screening instrument (14) in a real-world cardiac patient population by examining internal, construct and predictive validity. Results were threefold. First, factor analysis resulted in five separate constructs of psychosocial stress within the screener, reflecting comorbidity and some overlap between the theorized seven components (14). Second, the comparison of

the ultra-short and summarized screening items to matching full psychometric instruments resulted in fair to moderate agreement for depression, anxiety, and Type D personality. With respect to "work stress" and "marital stress", there was slight to fair agreement compared to matching validation instruments. For the detection of hostility, the ESC screener showed less than satisfactory performance. Finally, predictive validity was examined, showing that a positive screening result for depression, anxious tension, and Type D personality predicted angina and cardiopulmonary symptoms one year after PCI treatment, independent of respectively baseline angina NYHA class and baseline cardiopulmonary symptoms.

In contrast to the seven psychosocial factors of the ESC screener, chosen because of their evidence-based prognostic value (14), the current study reported a five-component structure. In the factor analysis, items from the "low SES" component loaded on the "work stress" and "social resources" components. This might imply that low SES is mainly important *in combination with* work stress and/or lack of social resources. Low SES might worsen cardiovascular diagnosis by acting as a predisposing factor for other kinds of psychosocial stress such as work stress (50). Moreover, in accordance with the original construct the two Type D components NA and SI loaded on different factors ("Emotional Distress" and "Social Stress"), with social inhibition clustering with social isolation, and NA clustering with depression, and anxiety items. However, it still is important to separately screen for depression, anxiety and NA for clinical and diagnostic purposes (51, 52). Although a redefinition of dimensions assessed by the ESC screener might be considered, we decided to maintain its seven-component structure for the purpose of the present paper.

For depression and anxiety, there was considerable sensitivity and good specificity in comparing ESC screening scores (at least 1 item positive) with scores on the PHQ-9 and GAD-7. Percentages of agreement were not affected by the acuteness of the event (PCI indication), or sex. The lower than ideal sensitivity for depression might be explained by the fact that depression in cardiac patients is sometimes less characterized by typical cognitive/affective symptoms (53). In addition, some cardiac patients may attribute depressive symptoms to their heart disease (54). Therefore, one may consider adding one or two somatic symptoms in a revision of the ESC screener. Using a more stringent criterion ("yes to both depression/anxiety ESC screening items"), as indicated by Kroenke et al. (32), resulted in considerable lower sensitivity but higher specificity.

While for anxiety and depression the ESC screener may be a useful instrument in clinical practice, these findings also lead us to advice a revision of the ESC instrument to improve screening of the other psychosocial risk markers. The ESC Screener assesses two personality constructs (i.e. Type D personality and hostility) and two sources of chronic stress (i.e. work stress & marital stress), which the current study has validated against full (original) questionnaires. We observed relatively poor concordance rates for presence or absence of these personality traits and stressors, in comparison to results for depression and anxiety.

The GAD-7 and PHQ-9 were developed to aid in the diagnosis of transient clinical states, with cut-offs signifying probable presence or absence of anxiety/depression. For personality characteristics a simple yes or no to two compiled questions derived from the full instrument (34) may not capture stable individual differences as well as the broader instrument. Notably, the endorsement of the social inhibition item in the ESC interview was relatively low, which is possibly related to the non-disclosing nature of patients scoring high on SI. Considering their potential social interaction anxiety (55), it is likely that verbally answering personal interview questions to a researcher, especially "Do you avoid sharing your thoughts and feelings with other people?" may make them feel more uncomfortable than completing a self-report questionnaire (55).

Concordance rates between the ESC screener and the hostility validation instrument were low. This might be explained by the fact that the 7-item Williams hostility subscale comprises items reflecting cynicism, aggressive responding, hostile attribution, and hostile affect (39). However, the ESC hostility items focus on hostile attributions and do not seem to cover the cynicism or aggressive responding facets of hostility. With respect to marital stress, the ESC screener performed poorly. There may be several reasons, relating to the question content, which may be overstated, leading to biases in endorsement percentages. Moreover, patients might be less forthcoming about relationship problems when interviewed, than when filling out a questionnaire. Finally, patients with a positive screen for work stress (especially on the effort/reward question) need further more in-depth and professional evaluation to correctly determine the actual presence of work stress. Based on these findings, we suggest some revisions that could improve sensitivity and reduce false negatives, including increasing the answering scale to a 4-point Likert scale and splitting up some questions that are currently asking multiple aspects of e.g. work stress or Type D in one question.

We also explored the predictive validity of the emotional distress component of the ESC screener, showing that a positive ESC screen on depression, anxious tension and Type D personality was associated with more angina and cardiopulmonary symptoms one year after PCI. This result is in concordance with results showing the prognostic qualities of the PHQ-4 (32), which differs from the screener only in answer categories. It is also in concordance with a previous study on Type D personality showing a prospective relationship with angina symptoms in post-MI patients (56).

In the current study, implementation of the 15-item psychosocial interview, immediately after treatment or one month after PCI (in acute patients) was relatively easy to achieve. However, screening is only useful when appropriate psychological care supports are in place (20, 21). Practically, the ESC screener is a simple, easy to use and low-cost instrument. To apply this instrument adequately in clinical practice, e.g., by nurses or cardiologists, basic guidelines from a mental health expert are needed. In a stepped care protocol (24), a positive screen on the (revised) ESC instrument in step 1 needs to be followed by more in depth

diagnostic assessments by skilled professionals. Tailored management can be arranged, e.g., in the context of cardiac rehabilitation, such as a consult with a specialized medical psychologist to correctly determine absence or presence of psychosocial problems, and install treatment if necessary.

Using the most predictive and informative items of original questionnaires seems to be a reasonable strategy to devise multidimensional screening tools, as the ESC workgroup tried to do. The depression and anxiety items of the ESC screener therefore actually match the PHQ-4 (32), which validly combines the core depression and anxiety symptoms. The PHQ-4 has been introduced relatively recently, and has not yet been used as often as the original instruments. In contrast, the personality and chronic stress items were composed by merging several items into one interview question. These items showed less than satisfactory congruence with the full instruments. Future research may want to examine which strategy results in the best screening question. An advantage of the ESC screening list compared to existing screening instruments, such as PHQ-9 (depression) and GAD-7 (anxiety), is its multidimensionality, making this instrument more comprehensive. Compared to existing multidimensional psychosocial screening instruments, such as the STOP-D (31), the ESC screener is more comprehensively assessing those constructs during a physicians' interview in clinical practice.

The results of the current study should be viewed in lights of its limitations and strengths. A major limitation is that all the instruments were self-report instruments, and did not include structured clinical interviews as a gold standard. However, only validated and widely-used questionnaires were used (e.g. PHQ-9 for depression and GAD-7 for anxiety) (29, 30). Addressing the need to identify cardiac patients who may need further psychosocial help more adequately, future research may include the comparison with a gold standard clinical interview. In the current study sample, 95% was Caucasian and 19% female, which is to be expected from a PCI sample in the Netherlands. However, it is important to examine sex and ethnic differences. Therefore, future research may include larger samples of women and different ethnic groups. Prevalence of emotional distress was relatively low in the current sample. Future research is needed to examine causes and consequences. The current results cannot be generalized to other cardiac patient groups, e.g. heart failure or atrial fibrillation. However, the interview might be useful in other cardiac patient groups as well. In the current study, we chose to administer the interview in an early stage (i.e. immediately after coronary treatment or 1 month later), and validity of the screening interview at other time points, e.g. during stable phases of the disease (e.g. one year after treatment) should be investigated in future work. Finally, the predictive value of depressive symptoms, anxiety and Type D for angina and cardiopulmonary symptoms was tested without adjustment for baseline angina and cardiopulmonary symptoms, so future research in larger samples is needed to examine whether it adds to routine assessment of angina and cardiopulmonary symptoms.

Key strength of the present study is its clearly defined patient population, representing an important part of the cardiovascular patients. The subsequent analyses in the current study are an important addition to the ESC guideline (14). In particular, the current study provides extensive validation results: considering (1) multiple psychosocial risk factors and (2) the predictive value of ESC screening scores with respect to angina and cardiopulmonary symptoms at one year follow-up.

In conclusion, the current ESC screener contributes to the search for a multidimensional and easy-to-use psychosocial screening instrument for cardiac patients. In its current version, it is not sufficiently valid to reliably detect the presence of all predefined psychosocial factors. However, positive screening scores for depression and anxiety might be useful in clinical practice. Positive ESC screens on depression, tension and Type D personality had considerable predictive value regarding cardiopulmonary and angina symptoms one year after PCI. Based on the current findings, suggestions for a revision and further validation of this instrument were made.

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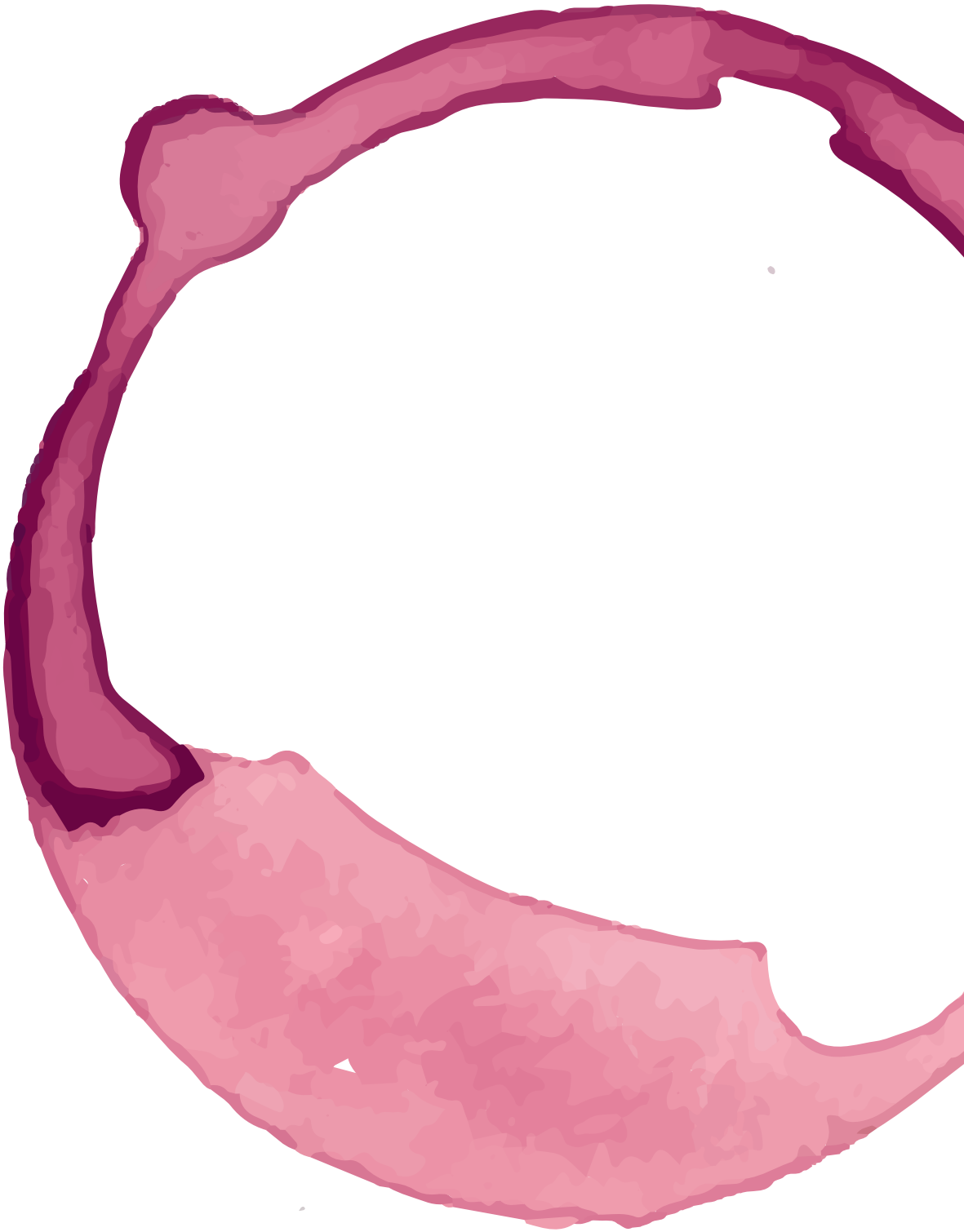
Supplementary Table. Analysis of ESC screening scores vs. validation instruments for Depression, Anxiety and Type D personality for men and women

Depression, n=364						
			men (n=301)		women (n=63)	
			no	yes	no	yes
ESC Screening instrument	"yes" to both depression items	no	268 (93%)	19 (7%)	50 (88%)	7 (12%)
		yes	5 (36%)	9 (64%)	1 (17%)	5 (83%)
	Sensitivity		.32		.38	
	Specificity		.98		.98	
	PPV		.64		.83	
	NPV		.93		.88	
			men (n=300)		women (n=66)	
			no	yes	no	yes
	"yes" to both anxiety items	no	266 (96%)	12 (4%)	53 (91%)	5 (9%)
		yes	13 (59%)	9 (41%)	4 (50%)	4 (50%)
	Sensitivity		.43		.44	
	Specificity		.95		.93	
	PPV		.41		.50	
	NPV		.96		.91	
			men (n=290)		women (n=63)	
			no	yes	no	yes
	"yes" to NA and SI items	no	232 (85%)	41 (15%)	53 (87%)	8 (13%)
		yes	8 (47%)	8 (53%)	0 (0%)	2 (100%)
	Sensitivity		.16		.20	
	Specificity		.97		1.00	
	PPV		.50		1.00	
	NPV		.85		.87	

ESC = European Society of Cardiology, PPV = positive predictive value, NPV = negative predictive.



Chapter 3

The tense, the hostile and the distressed: multidimensional psychosocial risk profiles based on the ESC interview in coronary artery disease patients – the THORESCI study

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ABSTRACT

Background: While single psychosocial factors have been associated with cardiovascular outcomes, it is still unclear how they cluster. Therefore, we examined whether latent multidimensional psychosocial risk profiles could be identified in the European Society of Cardiology (ESC) psychosocial screening interview. Additionally we examined whether these profiles were associated with specific characteristics.

Method: 681 cardiac patients (age=64.9±10.6; 80% men) completed the ESC interview, comprising 15 items on 7 predefined components. Multiple self-report questionnaires focusing on demographics, mood symptoms, personality, coping, and life events. Clinical information was extracted from patients' medical records.

Results: Latent class analysis identified four psychological classes: 1. Low psychological distress (62%), 2. High hostility (19%) 3. High tension (11%), 4. High psychological distress (8%), and two social classes: Low chronic stress (81%), and High work stress (%19). Characteristics increasing the odds to belong to the "High hostility" class were male sex, negative affectivity, and psychiatric history. "High tension" membership was associated with female sex, being single, a sedentary lifestyle, seeking social support, NA, early adverse life-events, depression, anxiety, and psychiatric history. "High psychological stress" characteristics were younger age, smoking, a sedentary lifestyle, NA, depression, anxiety, early adverse life-events, psychiatric history. Being younger, alcohol use and avoidance-oriented coping increased the odds to be in the "High work stress" class.

Conclusions: This study characterized four psychological and two social latent risk profiles. Results indicate the importance of a multidimensional psychosocial screening, potentially uncovering differential mechanistic pathways, which also may proof beneficial in clinical practice and in risk prevention strategies.

INTRODUCTION

Psychosocial distress contributes to the morbidity and mortality associated with cardiovascular disease (CVD) (1-6). Psychosocial factors that promote adverse cardiovascular events can be divided into two general categories: emotional factors and chronic stressors (5). Emotional factors include affective symptoms such as depression (7) and anxiety (8), but also more chronic, stable characteristics such as Type D personality (9), and hostility (10). Chronic stressors include low socio-economic status (11), work stress (11), and marital stress. All these factors may act through distinct psychobiological pathways that may be directly involved in the pathogenesis of CVD (12). Moreover, patients suffering from psychological distress demonstrate decreased well-being, poor health-related quality of life, and more treatment related complications (13, 14).

In previous work, psychosocial factors have mostly been studied as separate entities, while they often cluster (5). According to Suls and Bunde, this may be explained by the fact that they share underlying conceptual similarities (15). For example, anger, hostility, and anger expression (three well-known psychosocial correlates of cardiovascular disease) are not independent predictors, rather they form an "anger cluster" (15). In other research, "positive" psychosocial clusters, including multiple positive characteristics, and "negative" psychosocial clusters, including negative characteristics, were identified (16, 17). Other construct clusters exist as well, i.e., depression, anxiety, and negative affectivity (NA) are highly comorbid (18, 19). Moreover, low socio-economic status, chronic stress, depression, hostility, and social isolation often co-occur in cardiac patients (20-22). However, it is still unclear if and how other psychosocial factors cluster with the abovementioned factors in cardiac patient populations.

Considering cardiovascular outcomes, the effects of clustered psychosocial factors may differ from effects of single factors (4). Establishing multidimensional psychosocial profiles, covering multiple emotional factors (e.g., depression, anxiety, personality characteristics) and information about chronic stressors (14) may shed light on these complex relationships. Moreover, several domains of clinical, psychological, and social factors (which are important for the clinical management of patients), may predict to which multidimensional psychosocial profile a patient belongs (23). One may discriminate between clinical characteristics affecting presentation of a patient's symptoms (such as disease severity, medical interventions), and individual patients' psychological, and social vulnerabilities and resources. Contextual variables such as demographics (sex, age) and culture (ethnicity) are also important to consider, as they may influence the patients' perception of illness, coping styles, and psychological response to a cardiovascular event (24). Determining multidimensional psychosocial profiles and associated characteristics instead of single factors might increase the sensitivity of epidemiologic prediction models and clarify the pathophysiological pathways lining negative psychosocial states to cardiovascular conditions (25).

The current study therefore set out to investigate if and how multiple psychosocial factors, as assessed by the European Society of Cardiology's (ESC) psychosocial screening instrument, cluster together in a real-world cardiac patient population. We also aimed to further characterize the patients in the extracted psychosocial profiles through examining their demographic, clinical, lifestyle, and psychological characteristics.

METHODS

Patient population and procedure – the THORESCI study

The current study was part of a large prospective and ongoing observational cohort study, the "**T**ilburg **H**ealth **O**utcomes **R**egistry of **E**motional **S**tress after **C**oronary **I**ntervention (THORESCI)", which recruits participants from the clinical standard of care Percutaneous Coronary Intervention (PCI) Registry at the St. Elisabeth-TweeSteden Hospital in Tilburg, the Netherlands. All patients who were scheduled for either elective or acute PCI for one or more coronary occlusions were included. Patients needed to be adults and have sufficient understanding of the Dutch language to fill out questionnaires. Sufferers from life-threatening comorbidities (e.g., metastasized cancer) or cognitive disorders (e.g., dementia) were excluded. On the day of the PCI, patients were approached by a member of the research team who explained the study content and its requirements. After providing written consent, the patients were asked to fill out a set of validated psychosocial questionnaires, spread over five measurement moments post-PCI, i.e., immediately following PCI (within one week post-PCI), and at one and six months, one year and two years thereafter. For the current study, only questionnaire data completed within one month after PCI were used. Furthermore, the fifteen-item psychosocial European Society of Cardiology (ESC) screening interview was administered. The study protocol is in line with the Helsinki declaration and was approved by the institutional medical ethics review board (METC Brabant).

The ESC Psychosocial Screening Instrument

All patients underwent the face to face ESC psychosocial screening interview, either during hospital admission (elective PCI) or 1 month later (acute PCI). This fifteen-item, five minute interview was proposed by the European Society of Cardiology as an assessment of psychosocial problems (see Table 1), e.g., within the physicians' clinical interview (14). Three of the predefined components are tapping into social factors (seven items), such as (1) socio-economic status (i.e. educational level and manual worker), (2) work/family stress and (3) social isolation (i.e. living alone and having a close confidant). The other four

components (eight items) observe depression, anxiety, hostility, and Type D personality. The two depression questions are similar to the PHQ-2 with respect to content, not response scale (26). The two anxiety items are similar to the GAD-2, with respect to content (27). For the present study, the screening list was translated to Dutch, using the translation-back translation method. All fifteen questions are rated with "yes" or "no" by the interviewer, except the educational degree question, which has four response categories. In previous research, we investigated the validity of this interview (28).

Latent Class characteristics

Demographics Age, sex, marital status, work status and educational level were obtained from self-report questionnaires and patient's medical records at baseline. Marital status was recoded into two categories: with vs. without partner. *Clinical characteristics*, i.e., PCI indication (acute vs. elective), cardiac history (previous myocardial infarction (MI), percutaneous coronary intervention (PCI), and/or coronary artery bypass grafting (CABG)), concomitant cardiac diseases (atrial fibrillation, pacemaker, heart failure), comorbidities (cerebrovascular accident, transient ischemic attack, peripheral arterial disease, chronic obstructive pulmonary disease, kidney disease, rheumatoid arthritis, cancer, diabetes mellitus) risk factors (hypertension, hypercholesterolemia) were extracted from the patients' baseline medical records. *Lifestyle characteristics* included current smoking status, alcohol consumption, diet (variation, restriction of salt and saturated fats) and Body Mass Index and were obtained from self-report questionnaires. *Psychological characteristics* were assessed with self-report questionnaires, which were all psychometrically valid.

Type D personality was assessed with the 14-item Type D scale (DS14), covering two subscales, Negative Affectivity (NA; e.g., "I am often in a bad mood) and Social Inhibition (SI; e.g., "I often feel inhibited in social interactions), both consisting of seven items, rated on a five-point Likert scale from 0 ("false") to 4 ("true")(29).

For optimism, the Revised Life Orientation Test (LOT-R) was used. This questionnaire consists of ten positively and negatively worded statements and four "filler" items, all rated on a five-point Likert scale from 0 ("I disagree) a lot" to 4 ("I agree a lot") (30).

Stress resilience was determined with the 15-item hardiness scale (DRS-15). Items are rated on a four-point Likert scale from 0 ("false") to 4 ("true") (31).

The Coping Inventory of Stressful Situations (CISS) was used to measure how much patients engage in various coping activities during a stressful situation (32, 33). This instrument covers three 16-item scales assessing emotion-oriented coping, task-oriented coping and avoidance (distraction subscale and social subscale). All items are rated on a five-point Likert scale from 1 ("not at all") to 5 ("very strong").

For depression, the Patient Health Questionnaire (PHQ-9) was used (34). This measure consists of nine items, based on the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria of depression. Items are rated on a Likert scale from 0 ("not at all") to 3 ("almost every day") (34).

Anxiety symptoms were estimated using the Generalized Anxiety Disorder (GAD-7) scale, a tool to screen for generalized anxiety (35). The seven items are scored on a Likert scale from 0 ("not at all"), to 3 ("almost every day") (35).

Furthermore, Garnefski & Kraaij's Life Event Scale was administered (36). Included life events were long-lasting and/or severe physical or mental illness of self and/or significant others, death of a spouse and/or significant others, violence, abuse of drugs and/or alcohol within family and/or relationship. All events were assessed for three different periods of life, before the age of sixteen, between the age of sixteen and one year ago, and last year. For the purpose of the present study two dichotomous variables were created. The "mental illness of self" item was used to create a lifetime psychiatric history variable (0 "no psychiatric history" and 1 "psychiatric history"); all other items were used to create the early adverse life-events variable (0 "no early adverse life-events and 1 "early adverse life-event(s)") in which participants scored a 1 if items were endorsed for the event happening before the age of 16.

Statistical analyses

We performed a three-step latent class analysis in Latent Gold 5.1 (37). The first step involved building a latent class model by estimating models with an increasing number of classes. Both content considerations and information criteria -- the Bayesian information criterion (BIC), the AIC (Akaike Information Criterion) and the AIC3 – were used for model selection (38). An information criterion provides a quantitative index of the extent to which a model maximizes the correspondence between the observed and model-predicted responses while minimizing the number of parameters.

As a second step, for the selected model with the final number of classes, we added the class membership probabilities and the corresponding class assignments to our data file. For this we used the "modal classification method", which means that patients were assigned to the class with the largest posterior membership probability. By assigning patients to latent classes, also an estimate of the number of classification errors was obtained.

In the third step, we related a range of characteristics to the final latent classification scores saved in the second step to explore demographic, clinical, lifestyle, and psychological correlates of the classes. This was done using a multinomial logit model, taking into account the classification errors that were estimated in step 2 (39). It was tested whether characteristics were associated with class membership. Wald statistic was used as a test of significance. We

also performed post hoc Wald-tests to determine which specific class differences induced the main significant predictor effect. All possible paired class comparisons were tested (i.e. class 1 vs. class 2, class 1 vs. class 3, … , class 3 vs. class 4 etc.). Because of the large number of potential correlates and to show correlations with distinct groups of covariates, we estimated a separate model for each set of characteristics (i.e., demographic, clinical and psychological). To standardize psychological total scores we all transformed these to standard z-scores. We adhered to a significance level of $p<.05$. In Latent Gold 5.1, the output was described in log odds as compared to the first class. For interpretation purposes, we transformed all log odds values to odds, as displayed in the results table 4 and 5.

RESULTS

Sample characteristics

The current paper concerns those patients recruited for THORESCI between December 2013 and February 2016. Six hundred eighty-one participants (mean age=64.91 ± 10.6; 80% male) completed the ESC psychosocial screening interview within one month after PCI. Prevalence scores of endorsed screening items are displayed in Table 1. For step 1 and step 2 of the latent class analysis, all of these data were used. For step 3, ESC screener data, psychological questionnaire data and medical data were needed. These were available in a subset of this sample at the time of data extraction. Baseline characteristics are presented in Table 2.

Latent Class Analysis

Because a latent class analysis based on all eight psychological and all four social stress variables of the ESC screening resulted in a very large number of classes without a clear pattern, we decided to perform two separate analyses with the psychological (depression, anxiety, hostility and Type D symptoms) and the social variables (work and marital stress, socio-economic status and social isolation). Additionally, the association between psychological class membership and social class membership was estimated, using Pearson Chi Square analysis.

Psychological classes

Considering the lowest BIC, the best fitting model would have been a three-class model (Table 3). However, considering the AIC and AIC3 as well as the content of the classes, a four-class solution, was much more informative. As classes were sufficiently large, we opted for the 4-class model. The profiles of the four identified classes are displayed in Figure 1. Class 1,

Table 1. Questions and prevalence scores of the ESC Psychosocial Screening Interview (n=681)

Predefined Components	Items ESC Screening Instrument	Prevalence score (n)[1]	%
Low SES	1. What is your highest educational degree?		
	University, higher education, or equal	172	25
	Secondary education or equal	307	45
	Further education or equal	116	17
	Primary school (or less)	83	12
	2. Are you a manual worker?	136	20
Work/Family stress	3. Do you lack control over how to meet the demands at work?	79	12
	4. Is your reward inappropriate for your effort?	82	12
	5. Do you have serious problems with your spouse?	21	3
Social isolation	6. Are you living alone?	152	22
	7. Do you lack a close confidant?	37	6
Depression	8. Do you feel down, depressed, and hopeless?	107	16
	9. Have you lost interest and pleasure in life?	57	8
Anxiety	10. Do you frequently feel nervous, anxious, or on edge?	172	25
	11. Are you frequently unable to stop or control worrying?	154	23
Hostility	12. Do you frequently feel angry over little things?	180	27
	13. Do you often feel annoyed about other people's habits?	178	26
Type D personality	14. In general, do you often feel anxious, irritable, or depressed?	67	10
	15. Do you avoid sharing your thoughts and feelings with other people?	268	40

[1]prevalence of patients reporting "yes" to ESC interview questions; for all questions there were <1% missing values.

"Low psychological distress", reflected patients showing neither depression and anxiety complaints nor hostile and Type D characteristics (62%). Class 2, **"High hostility"**, comprised patients reporting high hostility, moderate anxiety (tension + worry) and moderate SI (19%). Class 3, **"High tension"**, was characterized by high tension, moderate mood complaints and moderate Type D characteristics (11%). Class 4, **"High psychological distress"**, consisted of patients showing overall heightened psychological symptoms (8%).

Social classes

Two classes were identified for social ESC screening symptoms in the best fitting model according to BIC, AIC, and AIC3 (Table 3). The profiles of the two identified classes are displayed in Figure 2. Class 1, **"Low chronic stress"** reflected patients showing neither work or martial stress, nor socio-economic stress or social isolation (81%). Class 2, **"High**

Table 2. Baseline Patient Characteristics and total scores for questionnaires (n=492*)

	N	%
Demographics		
Age (years)	65.2 (±9.5)	-
Men	400	81
Having a partner[a]	399	81
Working status[a]		
Currently employed	193	39
Retired	214	17
Unemployed or other	84	44
Clinical characteristics		
PCI indication		
Acute	333	68
Elective	159	32
Cardiac history	225	46
Concomitant cardiac diseases	34	7
Comorbidities[a]	158	32
Hypertension	201	41
Hypercholesterolemia	184	37
Lifestyle characteristics		
Smoking[a]	66	14
Alcohol[a]	320	66
Unhealthy diet[a]	9.01 (±2.36)	-
Sedentary lifestyle[a]	1.27 (±1.16)	-
BMI[a]	27.56 (±4.01)	-
	Mean	**SD**
Psychological characteristics		
Negative Affectivity[b]	7.5	5.6
Social Inhibition[b]	8.8	6.0
Optimism[b]	14.1	3.0
Resilience[c]	26.0	4.3
Coping styles[c]		
Emotion-focused	29.3	11.3
Task-oriented	44.7	13.8
Seeking social support	14.6	5.3
Avoidance-oriented	21.7	6.5
Depression[a]	4.4	4.2
Anxiety[a]	3.8	4.5
	N	**%**
Early adverse life-events[a]	122	25
Psychiatric history[a]	55	11

PCI = percutaneous coronary intervention; *patients who completed questionnaire within one month after they completed ESC screening at time of data extraction; [1]previous myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting; [a]≤1% missing values, [b]<2%, [c]15% missing values: some acute patients failed to fully complete questionnaire due to stressful coronary event and/or length survey.

work stress", consisted of patients reporting high levels of work stress (blue color worker + reward/effort imbalance + demand/control issues; 19% of total sample). Educational level, social isolation items (living alone + having a confidant) and marital stress were not distinctive for the classes.

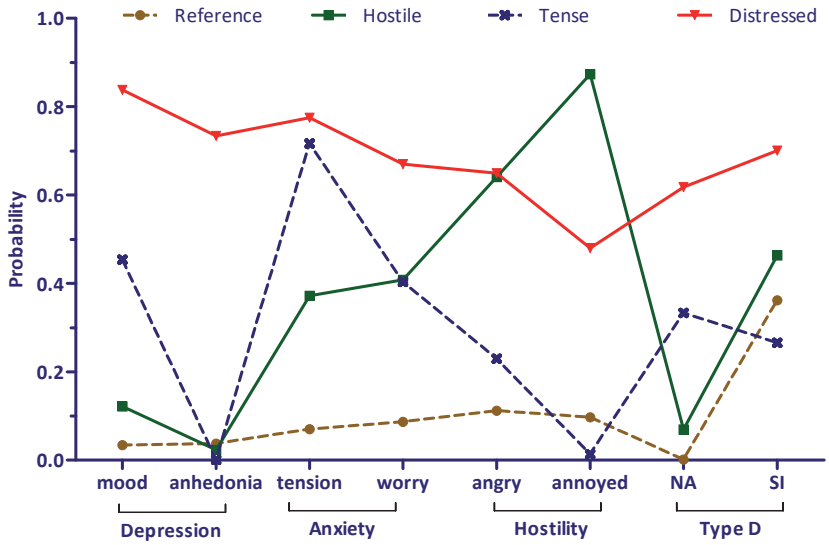

Figure 1. Psychological latent class profiles.
Note. NA = negative affectivity; SI = social inhibition.

Table 3. Identification of the number of latent classes using regression models for the elements of the ESC Screening instrument

	Statistics				
Model	LL	Npar	BIC	AIC	AIC3
Psychological symptoms					
1-Class	-2693.5244	8	5439.2373	5403.0488	5411.0488
2-Class	-2487.3700	17	5085.6405	5008.7400	5025.7400
3-Class	-2447.5366	26	5064.6858	4947.0732	4973.0732
4-Class	*-2428.2424*	*35*	*5084.8094*	*4926.4848*	*4961.4848*
Social symptoms					
1-Class	-1841.2043	7	3728.0735	3697.1041	3704.1041
2-Class	*-1737.1518*	*15*	*3572.1571*	*3505.0411*	*3520.0411*
3-Class	-1729.7365	23	3609.5149	3506.1476	3529.1476
4-Class	-1725.0288	31	3652.2880	3512.7194	3543.7194

Note. The chosen model is presented in italics. Fit was evaluated evaluating the content, the BIC, the AIC and the AIC3 as described in the Methods section. LL = log likelihood; Npar = number of estimated parameters.

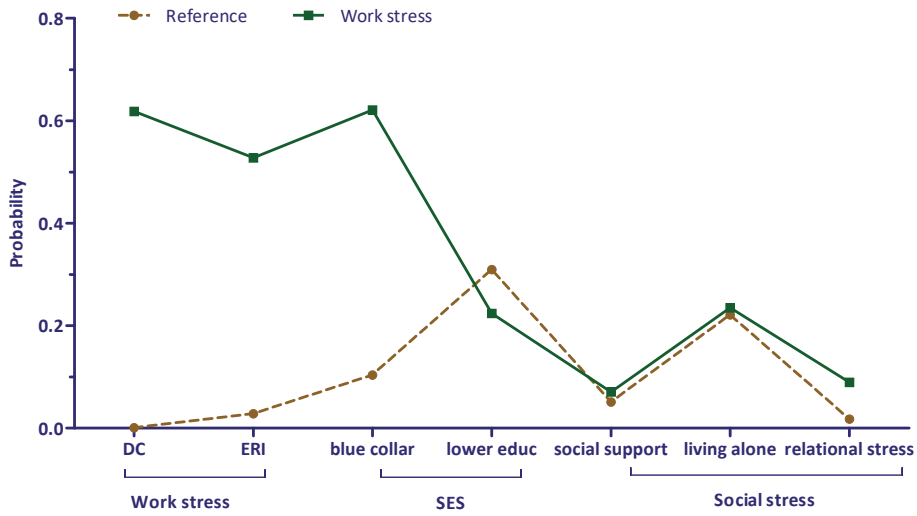

Figure 2. Social latent class profiles.
Note. DC = demand control issues; ERI = effort reward imbalance.

Characteristics of the Psychological classes

Table 4 shows the characteristics of the psychological distress classes and their associated odds difference, as compared to the reference class, which is **class 1 "Low psychological distress"**. Characteristics that increased the odds to be in the **"High hostility" class (class 2)** were male sex, NA, and psychiatric history. **Class 3 "High tension"** membership was associated with female sex, not having a partner, a sedentary lifestyle, the coping style "seeking social support", NA, early adverse life-events, depression and anxiety symptoms, and psychiatric history. **Class 4 "High psychological distress"** membership was associated with younger age, smoking, a sedentary lifestyle, NA, depression and anxiety symptoms, more early adverse life-events, and having a psychiatric history.

In post hoc class analysis, several other characteristics were associated with class membership, which, due to their relatively smaller effects, were not translated into a main significant effect. Considering **class 1 "Low psychological distress"** as the reference class, the emotion-focused coping style was associated with "High psychological distress" class membership. The avoidance coping style was associated with "High tension" class membership, while optimism decreased the odds to be in this "High tension" class.

Table 4. Association of multiple sets of covariates with psychological class membership

	Class 1 Low psychological distress (n=305)	Class 2 High-hostility (n=94)	Class3 High-Tension (n=54)	Class 4 High psychological distress (n=39)		
	Odds				Wald	p-value
Model 1. Demographics						
Age	1_{a}	$.99_{b}$	$.96_{a}$	$.93_{a,b}$	16.76	**.001**
Women	1_{a}	$.69_{b}$	$2.93_{a,b}$	1.10	10.73	**.013**
No partner	1_{a}	1.22_{b}	$3.06_{a,b}$	2.72	12.70	**.005**
Work status						.22
Unemployed	1	1.02	1.09	3.27	8.26	
Retired	1	.58	.97	2.23	.63	
Lower education (≤8 years)	1	1.09	1.17	1.32	.63	.89
Model 2. Clinical characteristics						
Acute PCI indication	1	.62	1.17	.56	5.09	.17
Cardiac history[1]	1	1.23	1.33	1.58	2.58	.46
Concomitant cardiac diseases[2]	1	.74	1.12	.81	.40	.94
Comorbidities[3]	1	.49	.86	.86	4.92	.18
Hypercholesterolemia	1	.86	1.34	1.30	1.57	.67
Hypertension	1	1.02	1.02	.86	.15	.98
Model 3. Lifestyle characteristics						
Smoking	1_{a}	$.67_{b}$	.10	$3.56_{a,b}$	9.61	**.022**
Alcohol	1	1.32	.88	2.14	3.18	.36
Unhealthy diet	1	.92	1.74	.76	5.86	.12
Sedentary lifestyle	$1_{a,b}$	1.40	1.90_{a}	1.80_{b}	17.45	**.0001**
BMI	1	1.00	.93	1.01	1.65	.65

Table 4. ***Continued***

	Class 1 Low psychological distress (n=305)	Class 2 High-hostility (n=94)	Class3 High-Tension (n=54)	Class 4 High psychological distress (n=39)	Wald	p-value
	Odds					
Model 4. Psychological characteristics + depression						
Negative Affectivity	$1_{a,b,c}$	$2.73_{a,d}$	2.95_{b}	$4.80_{c,d}$	39.05	**.000**
Social Inhibition	1	.71	.65	.76	.76	.49
Optimism	1	.92	.64	1.08	5.18	.16
Resilience	1	.86	.99	.84	.83	.84
Coping styles						
Emotion-focused	1	.23	1.05	2.03	5.80	.12
Task-oriented	1	.99	.78	.61	2.66	.45
Seeking social support	1_{a}	1.18_{b}	$2.36_{a,b}$	.91	7.98	**.047**
Avoidance-oriented	1	.80	.55	.96	6.30	*.098*
Early adverse life-events*	$1_{a,b}$	1.92_{c}	$3.40_{a,d}$	$10.29_{b,c,d}$	27.81	**.0001**
Depression	$1_{a,b}$	1.41_{c}	1.92_{a}	$2.73_{b,c}$	18.99	**.0001**
Model 5. Psychological characteristics + anxiety						
Negative Affectivity	$1_{a,b,c}$	2.55_{a}	2.30_{b}	3.70_{c}	26.03	**.0001**
Social Inhibition	1	.74	.74	.86	1.43	.70
Optimism	1	.89	.65	1.05	4.30	.23
Resilience	1	.83	.82	.64	2.62	.45
Coping styles						
Emotion-focused	1	1.89	.81	1.40	2.89	.41
Task-oriented	1	.96	.80	.68	1.61	.66
Seeking social support	1	1.10	2.04	.74	5.68	.13
Avoidance-oriented	1	.90	.67	1.24	3.52	.32

Table 4 continues on next page

Table 4. ***Continued***

	Class 1 Low psychological distress (n=305)	Class 2 High-hostility (n=94)	Class3 High-Tension (n=54)	Class 4 High psychological distress (n=39)		
	Odds				Wald	p-value
Early adverse life-events*	$1_{a,b}$	1.96_{c}	$3.83_{a,d}$	$12.23_{b,c,d}$	31.07	**.0001**
Anxiety	1_{a}	$1.46_{b,c}$	$2.66_{a,b}$	4.06_{c}	20.06	**.0001**
Model 6. Psychological characteristics + psychiatric history						
Negative Affectivity	$1_{a,b,d}$	$3.19_{a,c}$	4.13_{b}	$7.60_{c,d}$	49.43	**.0001**
Social Inhibition	1	.67	.63	.72	3.34	.34
Optimism	1	.98	.70	.12	3.13	.37
Resilience	1	.86	.97	.91	.46	.93
Coping styles						
Emotion-focused	1	1.33	1.09	2.23	5.54	.14
Task-oriented	1	.91	.81	.53	2.78	.43
Seeking social support	1	1.17	2.29	1.07	7.49	*.06*
Avoidance-oriented	1	.83	.59	.99	5.49	.14
Psychiatric history*	$1_{a,b,c}$	3.79_{a}	6.47_{b}	12.98_{c}	21.32	**.0001**

[1]previous myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, myocardial infarction, [2]atrial fibrillation, pacemaker, heart failure, 3cerebrovascular accident, transient ischemic attack, peripheral arterial disease, chronic obstructive pulmonary disease, kidney disease, rheumatism, cancer, diabetes mellitus; *dichotomous variables, Bold = p<.05, Italic = p<.01; Letters in subscript indicate significant differences between pairs of classes resulting from post hoc analysis.

Characteristics of the Social classes

Table 5 displays both social class and their associated odds differences. Characteristics that increased the odds to be in **class 2 "High work stress"**, were younger age, no history of cardiac diseases, fewer concomitant cardiac diseases, fewer non-cardiac comorbidities, more alcohol use and the avoidance-oriented coping style. An unhealthy diet and the seeking social support coping style are variables increasing the odds to **class 1 "Low chronic stress"** membership.

Table 5. Association of multiple sets of covariates with social class membership

	Class 1 Low chronic stress (n=400)	Class2 High work stress (n=92)		
	Odds		Wald	p-value
Demographics				
Age	1	.87	66.67	**.0001**
Women	1	.79	.40	.52
No partner	1	1.07	.04	.85
Clinical characteristics				
Acute PCI indication	1	1.70	2.83	*.092*
Cardiac history[1]	1	.40	11.43	**.001**
Concomitant cardiac diseases[2]	1	.01	47.67	**.0001**
Comorbidities[3]	1	.31	10.23	**.001**
Hypercholesterolemia	1	1.60	3.09	*.079*
Hypertension	1	.83	.42	.52
Lifestyle characteristics				
Smoking	1	1.67	2.09	.15
Alcohol	1	1.93	3.44	**.064**
Unhealthy diet	1	.65	9.63	**.002**
Sedentary lifestyle	1	1.22	1.78	.18
BMI	1	.95	1.71	.19
Psychological characteristics + depression				
Negative Affectivity	1	1.21	.77	.38
Social Inhibition	1	.99	.01	.93
Optimism	1	1.05	.10	.76
Resilience	1	1.12	.49	.48
Coping styles				
Emotion-focused	1	1.13	.31	.58
Task-oriented	1	1.11	.24	.62
Seeking social support	1	.64	5.04	**.025**
Avoidance-oriented	1	1.56	4.15	**.042**
Early adverse life-events*	1	1.70	3.01	*.083*
Depression	1	1.19	1.74	.19

Table 5 continues on next page

Table 5. ***Continued***

	Class 1 Low chronic stress (n=400)	Class2 High work stress (n=92)		
	Odds		Wald	p-value
Psychological characteristics + anxiety				
Negative Affectivity	1	1.27	1.11	.29
Social Inhibition	1	.99	.00	.69
Optimism	1	1.05	.07	.79
Resilience	1	1.11	.38	.54
Coping styles				
Emotion-focused	1	1.16	.41	.52
Task-oriented	1	1.09	.17	.68
Seeking social support	1	.63	5.18	**.023**
Avoidance-oriented	1	1.57	4.07	**.044**
Early adverse life-events*	1	1.73	3.31	*.069*
Anxiety	1	1.06	.13	.72
Psychological characteristics + psychiatric history				
Negative Affectivity	1	1.31	1.63	.2
Social Inhibition	1	.98	.02	.88
Optimism	1	1.06	.11	.74
Resilience	1	1.12	.45	.5
Coping styles				
Emotion-focused	1	1.13	.29	.59
Task-oriented 1	1	1.12	.32	.57
Seeking social support	1	.68	4.25	**.039**
Avoidance-oriented	1	1.50	3.65	*.056*
Psychiatric history*	1	1.69	1.82	.18

[1]previous myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting; [2]atrial fibrillation, pacemaker, heart failure; [3]cerebrovascular accident, transient ischemic attack, peripheral arterial disease, chronic obstructive pulmonary disease, kidney disease, rheumatism, cancer, diabetes mellitus; *dichotomous variables, Bold = p<.05, Italic = p<.01.

Association between Psychological and Social class membership

Table 6 shows the association between psychological and social class membership. Compared to the other psychological classes, patients in the "high hostility" class were most likely to be in the "high work stress" class (24%).

Table 6. Association between psychological and social class membership

		Social Classes	
		1. Low chronic stress (n=400)	2. High work stress (n=92)
Psychological Classes	1. Low psychological distress (n=305)	89% (404)	11% (49)
	2. High-hostility (n=94)	76% (91)	24% (28)
	3. High-Tension (n=54)	83% (55)	17% (11)
	4. High psychological distress (n=39)	79% (34)	21% (9)

DISCUSSION

The aim of the current analysis was to determine the ability of the ESC psychosocial screening instrument to identify subgroups of patients with coronary heart disease based on multiple psychosocial factors. Latent class analysis resulted in four subgroups of patients presenting similar psychological symptoms and two social stress classes. These findings add to the understanding of how the most important psychosocial factors interrelate.

With respect to psychological distress, patients could be characterized in four ways. Results further showed differences between the four classes on several demographic, lifestyle and psychological variables. Clinical variables were not distinctive for psychological class membership. The majority of the patients in the current sample displayed a "Low psychological distress profile" (Class 1). These patients reported minimal psychological symptoms and was therefore used as reference category. A second group showed a profile characterized by "High Hostility" (Class 2). This class consisted mainly of men, and reported NA and psychiatric history more often. A third psychological profile, "High Tension", mainly consisted of women. This profile was characterized by high anxious tension and low to moderate anxious worry and depression symptoms. Compared to class 1 and class 2, "High Tension" membership was associated with a higher psychological burden. Patients in this third group reported higher NA, more early adverse life-events, psychiatric history, and higher scores for depression and anxiety around PCI treatment. Furthermore, "High Tension" membership was associated with a sedentary lifestyle and being single. In stressful situations, patients in this subgroup tended to seek social support.

Remarkably, when comparing patients in the "High hostility" class with patients in the "High tension" class, substantial differences exist in their scores on anxious tension, but not on anxious worry. Previous work already accentuated the important difference between cognitive (e.g. worry) and somatic (e.g. tension) anxiety symptoms, both contributing to the pathophysiology of CVD through different psychobiological pathways (40). The current results confirm the important difference between different types of anxiety. Besides that

cognitive and somatic anxiety symptoms are associated with different pathways affecting cardiovascular health, they also represent distinct underlying patient groups, both associated with a specific set of characteristics.

Earlier studies have also shown important gender differences in psychosocial profiles in CVD patients, e.g. Consedine et al. showed that hostility predicts the presence of CVD in men while anxiety predicts CVD in women (41). Furthermore, it was found that psychological symptoms, such as depression, are more common among women than men (42), and that associations between somatic anxiety (e.g. tension) and CVD were stronger in women than in men (43). The fact that patients in the "High Tense" class more often reported "seeking social support" as coping mechanism to handle stressful situations may be explained by the fact that this class mainly comprised women who do not have a partner, and might seek social support outside the family. In single women, who are suffering from somatic and/or psychological symptoms, reinforcement of social support (with our without professional help) might reduce their stress levels (44).

The fourth psychological class, "High psychological distress", reflected a relatively small subset of patients showing a profile of overall high psychological distress around their PCI treatment. More specifically, they reported high depression symptoms (mood and anhedonia), high anxiety symptoms (tension and worry), high anger and moderate to high annoyance. Patients in this class also displayed high scores on both Type D personality constructs (NA and SI), which were only low to moderate in the other three classes. This supports previous findings showing that NA is an important personality correlate of psychiatric disorders, as it is highly correlated with symptoms and diagnoses of both anxiety and depression (19). Moreover, NA is a general trait of somato-psychic distress, which is expressed through a broad range of negative mood states and somatic complaints (45). Compared to the other classes, patients in this "High distress" class were younger, had the highest levels of psychological burden and had an unhealthy lifestyle (more smoking, sedentary lifestyle). Earlier work already highlighted that an unhealthy lifestyle (more frequent smoking, less physical activity) is one of the mechanisms linking psychosocial factors to CVD (46).

Two social classes were determined: (1) Low chronic stress and (2) High work stress. This latter comprised blue collar workers lacking control over how to meet the demands at work with a disrupted effort-reward balance. Patients with high work stress were younger and consumed alcohol more frequently. Psychologically, none of the characteristics were associated with the "High work stress" subgroup, except that in the "High work stress profile" the avoidance-oriented coping style was more common (e.g., trying to sleep, shopping or watching television to cope with stressful situations). Importantly, in contrast to the psychological classes, for the two social classes, clinical characteristics were distinctive. Patients with high work stress more often had a first-time, often acute, event in the absence of a cardiac history and non-cardiac comorbidities, but with classic risk factors such as

hypercholesterolemia. Additional analysis showed that compared to the other psychological classes, patients in the "High hostility" class were most likely to be in the "High work stress" class, although overlap was limited to a quarter of the total study population.

The current findings indicate the importance of assessing both psychological and social factors in patients with coronary artery disease. Previous studies have focused on clustering of mood constructs mostly (1, 17, 25, 47, 48). Only recently, a study was published in which a broader range of constructs were introduced in a cluster analysis, resulting in a social cluster and a distress cluster (49). The fact that we needed to separate our latent class analysis for the psychological and social stress variables, is in agreement with this latter finding. It is important to discriminate between a cluster analysis and a latent class analysis though. While cluster analysis clusters constructs with an unobservable shared source of variance (as in the above mentioned studies), latent class analysis identifies unobservable subgroups of people in a population. The currently distinguished latent patient groups, with comparable multidimensional scoring profiles, extend the already previously revealed knowledge about clustered psychosocial constructs.

Besides that information about subgroup membership and its associated characteristics is useful in the understanding of the complex pathways between psychosocial functioning and CVD. This knowledge may also be helpful in clinical practice, for example in tailoring interventions to target subgroups that will benefit most. The current study results showed that highly distressed patients tended to use emotion focused coping strategies, while the tense and hostile subgroups were more likely to seek social support. For psychological interventions, for example during cardiac rehabilitation, coping style preferences may be informative in choosing an appropriate therapeutic approach. Importantly, the reference group seemed to use task-oriented and avoidance coping a bit more, the latter of which is concurrent with the fact that they were also slightly (non-significantly) more likely to feel socially inhibited. This might mean that a subgroup of the reference group patients was less willing to endorse the presence of social or emotional stress due to their social inhibition.

Furthermore, the current study results can be helpful in tertiary risk prevention strategies. Patients with a high work stress profile were for example of younger age, had fewer comorbid illnesses, fewer cardiac history and fewer concomitant cardiac diseases. Patients with this profile reported a relatively unhealthy lifestyle with respect to alcohol and (to a lesser extent) tobacco use. It seems that in this subgroup mainly modifiable risk factors may adversely affect cardiovascular prognosis. For these patients, future studies should determine whether intervening on lifestyle, cardiovascular risk management, and stress management might improve their longer term cardiovascular risks. In any case, they should be treated differently from the high psychological distress subgroup, who were more likely to be unemployed or retired, in which emotional problems such as depression, anxiety, and psychiatric history play a much more important role, and should be their focus of treatment.

The results of the current study should be viewed in light of its strengths and limitations. Key strength of the present study is its clearly defined and relatively large patient population, representing an important part of the cardiovascular population. The fourth psychological class, covering highly distressed patients, was relatively small. Including larger samples in future work might give more information about this high-risk group. In this study, information about psychological functioning (anxiety, depression, Type D personality, coping, psychological history) was assessed via self-report instruments, which may not reflect actual psychological functioning. However, only validated and widely-used questionnaires were used (34, 35). Furthermore, the face-to-face ESC screening interview was used, which might be sensitive for social desirability. However, an important strength of this instrument is its multidimensionality.

In conclusion, the current study results give more insight in the latent psychosocial profiles in coronary heart patients, revealing four psychological and two social latent profiles, all associated with specific characteristics. Therefore, it seems advisable to use a multidimensional psychosocial screening instrument, covering multiple cognitive-emotional factors and chronic stressors, instead of just information on for example depression and anxiety. Future research should determine whether the same profiles are distinguished using full-sized, standardized psychological questionnaires. These and future findings might be helpful in clarifying pathways between psychosocial states and cardiovascular conditions, in clinical practice (e.g., in stepped-care when referring patients to appropriate and tailor-made treatment), but also in risk prevention strategies (e.g., in identifying subgroups associated with modifiable risk factors, such as an unhealthy lifestyle).

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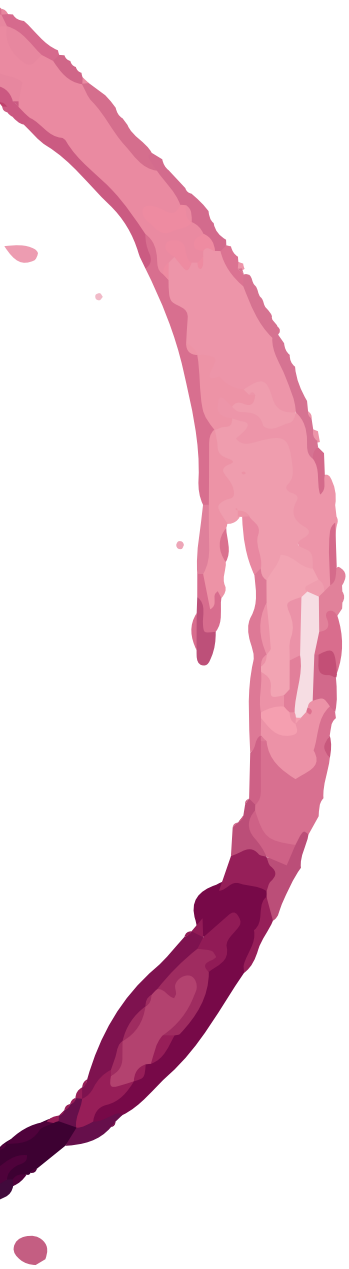

Chapter 4

Person–centered analysis of psychological traits to explain heterogeneity in patient–reported outcomes of coronary artery disease – the THORESCI study

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ABSTRACT

Background: Heterogeneity in the prognosis of coronary artery disease (CAD) patients may be explained by relatively stable individual psychological differences. Therefore, we studied multiple personality and coping traits using a person-centered approach, and examined the predictive value of this approach for patient-reported outcomes.

Method: 657 CAD patients (age=66.39±10.6; 79% men) completed multiple self-report questionnaires focusing on demographics, negative affectivity and social inhibition (DS14), neuroticism and extraversion (EPQ), resilience (DRS-15), and coping styles (CISS) after undergoing percutaneous coronary intervention. Depressive symptoms (PHQ-9), anxiety (GAD-7), and treatment adherence (MOS) were assessed at six months follow-up. Clinical information was extracted from patients' medical records.

Results: A step-3 latent class analysis identified four subgroup profiles: *Low distress* (31%), *Passive coping* (21%), *Active coping* (20%), and *High distress* (28%). For all patient-reported outcomes, overall significant differences between the subgroups were observed (p-values <.05). The *High distress* profile was associated with the highest levels of emotional distress (d's>.94), and lowest levels of positive mood (d=-1.02) and treatment adherence (d=-2.75) at follow-up. Patients with an *Active coping* profile also experienced increased emotional distress (d's>.50), but participated in cardiac rehabilitation most often (d=.13), and reported high levels of positive mood (d=-1.02). Patients with a *Passive coping* profile displayed few emotional problems after six months (d's<.30), but participation to cardiac rehabilitation was relatively low (d=.04).

Conclusions: This study revealed four distinct psychological latent subgroups, which were predictive of patient-reported outcomes. The results indicate that a person-centered approach is useful in explaining heterogeneity in recovery from PCI, and may enhance personalized medicine in patients with CAD.

INTRODUCTION

Psychosocial factors have been associated with the morbidity and mortality of coronary artery disease (CAD) (1-3). Several recent meta-analyses have indicated that negative emotions, such as depression (4) and anxiety (5), but also more stable traits, such as Type D personality (combination of negative affectivity and social inhibition) (6, 7), are associated with adverse events and mortality. In addition, chronic stressors, such as a lower socio-economic status (8) and a lack of social support (9) may worsen CAD. However, these meta-analyses also reported substantial heterogeneity in when and how psychosocial factors affect the prognosis of CAD. While several studies in CAD patients showed an association between psychosocial factors, such as anxiety and depression, with major adverse cardiovascular events during follow-up (10, 11), other studies did not find these associations (12). Moreover, a recent study showed large heterogeneity in the prognostic value of individual depressive symptoms in patients with CAD across sex and age subgroups (13).

This heterogeneity may have several causes, including age differences, comorbid medical conditions and other differences in study characteristics (14). The risk of adverse events is already higher in older patients due to an aging heart and age-associated conditions, such as kidney disease and anemia (15-17). Furthermore, the choice of endpoint is a crucial determinant of the prognostic effect of a risk factor (18). For example, a recent study showed that Type D personality may be more related to fatal and non-fatal cardiac events than to all-cause mortality, and has different effects in different age-groups (19).

Heterogeneity in clinical outcomes may also be explained by relatively stable individual differences in personality (20). Specific sets of interrelated thoughts, feelings, and behaviors might affect the propensity to experience lower or higher levels of psychological distress (20). Patients scoring high on neuroticism are more vulnerable to experience negative emotions such as anxiety, depression, and anger after a cardiac event (21). In contrast, resilient patients seem to report better emotional and physical well-being at follow-up (22). Furthermore, patients' coping styles, which can be defined as relatively permanent, individual-specific ways of facing difficulties in stressful situations, may play a role in this context (23, 24). While coping originally was described as a dynamic process, most researchers over the past decades have operationalized coping as trait-like strategies. Coping styles or "defenses" are involuntary behaviors that are used to shield from sudden changes, in this case the cardiac event (25, 26). There are several approaches to classify coping styles. They can be allocated according to level of maturity, where immature defenses include behaviors such as projection, while sublimation or humor are considered mature defenses (25, 26). Another perspective distinguishes different categories of coping styles, such as emotion-focused (e.g. blame myself for procrastinating) and task-oriented coping (e.g. outline my priorities). Whether coping styles are adaptive or maladaptive depends on the situational context.

Most research on personality and coping styles is based on a *variable-centered* approach, which strives to group similar variables or "traits" together. This approach assumes that the population is homogeneous in how these traits operate on outcomes (27, 28). A *person-centered* approach aims to identify groups of individuals who share particular attributes or show similar scoring "profiles" (27, 28). A profile captures unique personality information that is not well covered by the use of multiple trait scores (29). Identifying profiles based on relatively stable traits might be helpful for a better understanding of the heterogeneity in psychosocial characteristics that may affect the clinical course of CAD, but also for personalized medicine, which aims to individualize care according to the patients' unique characteristics (30-32).

The aim of the current study was to apply a person-centered approach to personality traits and coping styles based on latent class analysis in patients with CAD. We also examined the predictive value of this approach in explaining heterogeneity in patient-reported outcomes at six months follow-up.

METHODS

Patient population and procedure – the THORESCI study

The current study was part of a large prospective and ongoing observational cohort study, the **T**ilburg **H**ealth **O**utcomes **R**egistry of **E**motional **S**tress after **C**oronary **I**ntervention (THORESCI), which recruits participants from the clinical standard of care Percutaneous Coronary Intervention (PCI) Registry at the St. Elisabeth-TweeSteden Hospital in Tilburg, the Netherlands. All patients who were scheduled for either elective or acute PCI for one or more coronary occlusions were included. Eligible patients were adults and had sufficient understanding of the Dutch language to fill out questionnaires. Patients with life-threatening comorbidities (e.g., metastasized cancer) or severe cognitive disorders (e.g., dementia) were excluded. On the day of the PCI, patients were approached by a member of the research team who explained the study content and its requirements. After providing written consent, the patients were asked to fill out a set of validated psychosocial questionnaires, spread over five measurement moments post-PCI, i.e., immediately following PCI (within one week post-PCI), at one and six months, one year and two years thereafter. For the current study, questionnaire data completed within one month and on six months after PCI were used. The study protocol is in line with the Helsinki declaration and was approved by the institutional medical ethics review board (METC Brabant).

Personality and coping characteristics

Negative affectivity (NA) and social inhibition (SI) – Both NA and SI were assessed with the 14-item Type D scale (33). Seven NA (e.g., "I am often in a bad mood") and 7 SI (e.g., "I often feel inhibited in social interactions) items are rated on a 5-point Likert scale from 0 (false) to 4 (true). In the current study, internal consistency for NA and SI was high (Cronbach alpha at .88 for SI and NA).

Neuroticism and Extraversion – To assess neuroticism and extraversion, two subscales of the Eysenck Personality Questionnaire (EPQ) were used (34): the neuroticism subscale (e.g., "Does your mood often go up and down?") and the extraversion subscale (e.g., "Do you enjoy meeting new people?"). Both subscales comprise 12 items and are rated on a dichotomous (yes/no) scale. In the current study, internal consistency for both subscales was high (Cronbach alpha at .86 for neuroticism and at .85 for extraversion).

Social interaction anxiety – Social interaction anxiety was evaluated using the Social Interaction Anxiety questionnaire (35). Ten items (e.g., "I have difficulty making eye contact with others") are rated on a 5-point Likert scale from 0 (not at all characteristic of me) to 4 (extremely characteristic of me). In the current study, internal consistency was excellent (Cronbach alpha .93).

Resilience – Resilience was evaluated using the Dispositional Resilience Scale (DRS15) (36). This 15-item scale assesses hardiness, which is a personality or cognitive style linked to good health and performance in stressful situations and comprises three components: challenge (i.e. seeing change and new experiences as exciting opportunities to learn and develop), commitment (i.e. tendency to see the world as interesting and meaningful) and control (i.e. belief in one's own ability to control or influence events) (36). Items (e.g., "I like the challenge of having to do many things at once") are rated on a four-point Likert scale from 1 (don't agree at all) to 4 (totally agree). In the current study, the DRS15 showed adequate internal consistency (Cronbach alpha at .70).

Coping styles – The Coping Inventory of Stressful Situations (CISS) was used to measure which coping styles patients use during a stressful situation (37, 38). The CISS comprises four coping styles: emotion-focused (16 items, e.g. "blame myself for procrastinating"), task-oriented coping (16 items, e.g., "outline my priorities"), distraction (10 items, e.g., "take time off and get away from the situation") and seeking social support (6 items, e.g., "visit a friend"). All items are rated on a five-point Likert scale from 1 (not at all) to 5 (very strong). In the current study, internal consistency was high (Cronbach alpha at .92 for emotion-focused coping, at .94 for task-oriented coping, .84 for seeking social support and at .79 for distraction).

Patient–reported outcomes

Anxiety – To assess whether patients experienced anxiety symptoms during the past two weeks, the Generalized Anxiety Disorder (GAD-7) scale was used (39). The 7 items of this valid and efficient tool to screen for generalized anxiety are scored on a Likert scale form 0 (not at all), to 3 (almost every day). The recommended cut-off score is ≥10. In the current study, internal consistency was excellent (Cronbach alpha .92).

Depression – To assess whether patients experienced depressive symptoms during the past two weeks, the reliable and valid Patient Health Questionnaire (PHQ-9) was used (40). This measure consists of 9 items (e.g., "Little interest or pleasure in doing things"), based on the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria of depression. Items are rated on a Likert scale from 0 (not at all) to 3 (almost every day). In the present study, the internal consistency of the PHQ-9 was high (Cronbach alpha at .88).

Positive mood and negative mood – Positive and negative mood as experienced during the past few weeks were assessed using the Global Mood Scale (GMS) (41). This instrument comprises two subscales with ten positive mood terms (e.g., "lively" and "bright") and 10 negative mood terms (e.g., "fatigued" and "listless"), respectively. Items are rated on a five-point Likert scale from 0 (not at all) to 4 (extremely). In the current study both scales had high internal consistency (Cronbach alpha positive mood .88; Cronbach alpha negative mood .89).

Adherence

At six months post-PCI, adherence behavior during the past four weeks was assessed using the Medical Outcomes Study (MOS) questionnaire (42). For *general treatment adherence* the first part of the MOS was used. This subscale comprises 5 items (e.g., "I followed my doctor's suggestions exactly"). In the present study, this subscale had adequate internal consistency (Cronbach alpha = .69). For *cardiac rehabilitation participation* 2 other items of the MOS were used ("How often did you take your prescribed medication?" and "How of did you take part in a cardiac rehabilitation program"?). All items were rated on a 6-point Likert scale from 1 (never) to 6 (always).

Demographic and Clinical variables

Demographic and medical variables were obtained from self-report questionnaires and patients' medical records at baseline. These included age, sex, marital status, working status, PCI indication (acute vs. elective), cardiac history (previous myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, and/or myocardial infarction), concomitant cardiac diseases (atrial fibrillation, pacemaker, heart failure),

comorbidities (cerebrovascular accident, transient ischemic attack, peripheral arterial disease, chronic obstructive pulmonary disease, kidney disease, rheumatism, cancer, diabetes mellitus) and risk factors (hypertension, hypercholesterolemia).

Statistical analyses

A *variable-centered* exploratory factor analysis was performed in SPSS 22 (IBM SPSS Statistics for Windows, Version 22. Armonk, NY: IBM Corp USA) to explore the construct validity of the measured personality and coping traits, and this was used to create a framework for the *person-centered* latent class analysis. The underlying relationships between the measured constructs were identified by the principal axis factoring method, calculating Catell's scree test and Eigenvalues (>1.0) (43). Subsequently, we entered the personality and coping traits in the latent class analysis by using the sequence of the constructs as extracted by the factor analysis.

A step-3 latent class analysis was conducted to examine the existence of a discrete number of different subgroups in terms of relatively stable psychological profiles, in Latent Gold 5.1 (44). The latent class model was built by estimating models with an increasing number of subgroups. The variables with negative loadings in the factor analysis, resilience and extraversion, were reversed to low resilience and introversion for interpretation purposes. Information criteria – the Bayesian information criterion (BIC), the AIC (Akaike Information Criterion) and the AIC3 – were used to choose the most parsimonious and best fitting model (45). Content considerations were used to decide between models when an additional latent class had little substantive meaning (46).

For the selected model with the final number of subgroups, we added the subgroup membership probabilities and the corresponding subgroup assignments to our data file. For this we used the modal classification method, which means that patients were assigned to the subgroup with the largest posterior membership probability. E.g., a patient that belongs for 20% to one subgroup, for 30% to another, and for 50% to a third subgroup, will be assigned to the third subgroup. By assigning patients to latent subgroups, also an estimate of the number of classification errors was obtained.

Additionally, we related a range of characteristics to the final latent classification scores to explore demographic and clinical correlates of the subgroups. This was done using a multinomial logit model, taking into account the estimated classification errors (47). Wald statistics were used as a test of significance. We also performed post hoc Wald-tests to determine which specific subgroup differences induced the main significant effect. All possible paired subgroup comparisons were tested post-hoc (i.e. subgroup 1 vs. subgroup 2, subgroup 1 vs. subgroup 3, … , subgroup 3 vs. subgroup 4 etc.). In Latent Gold 5.1, the output was described in log odds as compared to the first class. For interpretation purposes, we transformed all log odds values to odds, as displayed in the results table 4. An odds of

3 to 1 means one patient has the characteristic for every three patients that don't have the characteristic in that subgroup.

Finally, we related the final latent classification scores with multiple 6-month outcomes, also using a multinomial logit model. We did not correct for covariates in this final step as this is not possible in the 3-step latent class analysis, but the choice to analyze prediction models in Latent GOLD meant that the estimated classification errors were taken into account (47). Wald statistics were used to estimate the main and post-hoc effects. We adhered to a significance level of $p<.05$. Cohen's d effect sizes were calculated to compare the difference in means divided by the average of standard deviations of the subgroups in relation to the reference group. Cohen suggested that d=0.2 be considered a "small" effect size, 0.5 a "medium", and 0.8 a "large" effect size (48).

RESULTS

Sample characteristics

The current paper concerns those patients recruited for THORESCI between December 2013 and July 2016 (n= 657; mean age=66.3 ± 10.8; 79% men). Baseline characteristics and prevalence scores are displayed in Table 1.

Table 1. Baseline characteristics of patients with CAD (n=657)

Demographics	N	%
Age (years ± SD)	66.31 ± 10.82	-
Men	517	79
Having a partner[a]	543	83
Working status[a]		
Currently employed	256	39
Retired	278	42
Unemployed or other	121	19
Clinical characteristics	**N**	**%**
PCI indication		
Acute	467	71
Elective	190	29
Cardiac history[1]	348	53
Concomitant cardiac diseases[2]	34	5
Comorbidities[3]	193	29
Hypertension	260	40
Hypercholesterolemia	250	38

Table 1 continues on next page

Table 1. ***Continued***

Personality and coping characteristics	Mean	SD
Negative Affectivity[b] (0-28)	7.5	5.9
Social Inhibition[b] (0-28)	8.8	6.2
Neuroticism[c] (0-12)	2.9	3.1
Introversion[c] (0-12)	4.8	3.4
Low resilience[d] (15-60)	17.7	5.7
Social Interaction Anxiety[a] (0-40)	3.1	5.1
Task-oriented coping[a] (16-80)	44.5	13.6
Distraction coping[a] (10-50)	21.8	6.7
Social support coping (6-30)	14.7	5.3
Emotion-focused coping[a] (16-80)	29.2	11.0

PCI = percutaneous coronary intervention; [1]previous myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting; [2]atrial fibrillation, pacemaker, heart failure, [3]cerebrovascular accident, transient ischemic attack, peripheral arterial disease, chronic obstructive pulmonary disease, kidney disease, rheumatism, cancer, diabetes mellitus; [a]≤1%, [b]≤2%, [c]≤4%, [d]≤5% missing values: some acute patients failed to fully complete questionnaire due to stressful coronary event and/or length survey.

Variable–centered approach: factor analysis

All ten personality characteristics and coping styles were subjected to principal component analysis. Inspection of the correlation matrix revealed the presence of many coefficients of .25 and above. The Kaiser-Meyer-Olkin value was .75, exceeding the recommended value of .6 and the Barlett's Test of Sphericity (49, 50) reached statistical significance, supporting the factorability of the correlation matrix. There were three components with eigenvalues exceeding 1 and the scree plot (51) also showed a break (elbow) around the third component. Varimax rotation was performed to aid in the interpretation of these components, resulting in three components with strong loadings (Table 2). The first component, "Negative affectivity", comprised negative affectivity, neuroticism and lack of stress resilience. Three coping styles, seeking social support, distraction and task-oriented coping strongly loaded on the second component, "Coping". Third, the "Inhibition" component, consisted of social inhibition, extraversion (reversed) and social interaction anxiety. Emotion-focused coping loaded positively on two factors (.78 on factor 1 and .51 on factor 2) and this variable was not included in further analyses.

Table 2. Dimensions of personality and coping characteristics measured at baseline

		Components Factor Analysis		
		Dimensions		
		1.Negative affectivity	2. Active Coping	3. Inhibition
Negative affectivity	(DS14)	**.80**	.01	.28
Neuroticism	(EPQ)	**.81**	.08	.21
Resilience	(DRS15)	**-.70**	.18	-.17
Emotion-focused coping	(CISS)	.76	.51	.11
Seeking social support coping	(CISS)	.07	**.83**	-.19
Task-oriented coping	(CISS)	-.08	**.82**	.13
Distraction coping	(CISS)	.19	**.82**	-.09
Social inhibition	(DS14)	.22	-.01	**.88**
Extraversion	(EPQ)	-.10	.14	**-.84**
Social interaction anxiety	(SIAS)	.38	.07	**.69**
Eigenvalues		4.31	2.56	1.18
% of variance explained by the component		39	23	11

DS14 = Type D scale 14, EPQ = Eysenck Personality Questionnaire, DRS15 = Dispositional Resilience Scale, CISS = Coping Inventory of Stressful Situations, SIAS = Social Interaction Anxiety Scale; Factor loadings of traits scales assigned to a factor (loading ≥.60 on one factor and <.40 on the other factors) are presented in bold.

Person–centered approach: Latent Class Analysis

The best fitting model

To select the best fitting latent class model, results of models with a subsequent number of classes (1-6) were compared (Table 3). The lower the BIC value, the better a particular model is (47). However, from Table 3 it can be observed that all fit indicators continue to drop until the six-class model. We compared the content of the subgroups in the two- to six-class models and decided to opt for the four-class model, because additional latent classes had little substantive meaning (46). The profiles of the identified subgroups are displayed in Figure 1. The three components that were extracted from the previous analysis (Negative affectivity, Coping, and Inhibition) were used as a framework to describe the profiles of the four subgroups. Remarkably, within each profile, levels for all three coping styles (social support, distraction, and task-oriented coping) were all high, all low or all moderate and were therefore interpreted in terms of active vs. passive. Furthermore, stress resilience levels were similar for all profiles.

Table 3. Number of latent subgroups based on regression models of personality and coping characteristics

	Statistics				
Model	LL	Npar	BIC (LL)	AIC (LL)	AIC3 (LL)
1-Class	-18250.0782	18	36616.9348	36536.1565	36554.1565
2-Class	-17186.3711	37	34612.7866	34446.7423	34483.7423
3-Class	-16863.3670	56	34090.0443	33838.7340	33894.7340
4-Class	-16669.7659	75	33826.1082	33489.5319	33564.5319
5-Class	-16548.5554	94	33706.9530	33285.1107	33379.1107
6-Class	-16411.9955	113	33557.0992	33049.9909	33162.9909

The chosen model is presented in italics. Fit was evaluated evaluating the BIC and content of the classes as described in the Methods section. LL = log likelihood; Npar = number of estimated parameters.

The first subgroup comprised patients with a *Low distress* profile, as indicated by low scores on the traits of the negative affectivity and inhibition dimension (31%). Patients in the *High distress* subgroup (28%), displayed an opposite profile, scoring high on both the negative affectivity and inhibition dimension. Both the *Low distress* and the *High distress* subgroup reported moderate scores on the coping dimension. A third subgroup was defined by patients with a Passive coping profile (21%), showing low scores on the coping traits and increased introversion. Fourth, patients with an Active coping profile (20%) reported high scores for the coping dimension and increased negative affectivity.

Background characteristics of the subgroups

Table 4 shows prevalence of anxiety, depression, and Type D personality in the four subgroups. Moreover, this table shows the characteristics of the subgroups and their associated odds difference, as compared to the *Low distress* subgroup. Patients in the *High distress* subgroup were more often single and less often retired. Patients with a *Low distress* profile were most often retired. *Active coping* membership was associated with being unemployed. There were no significant differences in age and sex between the groups. Regarding clinical characteristics, only a trend was observed for the presence of comorbidities, with post-hoc class analysis showing that patients with an *Active coping* profile had less comorbidities than patients in the *Low distress* subgroup (Wald=6.16; p=.013).

Subgroup membership and patient–reported six–month outcomes

Figure 2 shows the four subgroups and the associated mean scores for multiple six-month outcomes. The Wald statistics and p-values, showed overall significant differences between the subgroups for all patient-reported outcomes (anxiety, depression, negative and positive mood, treatment adherence, rehabilitation participation). Table 5 displays the effect

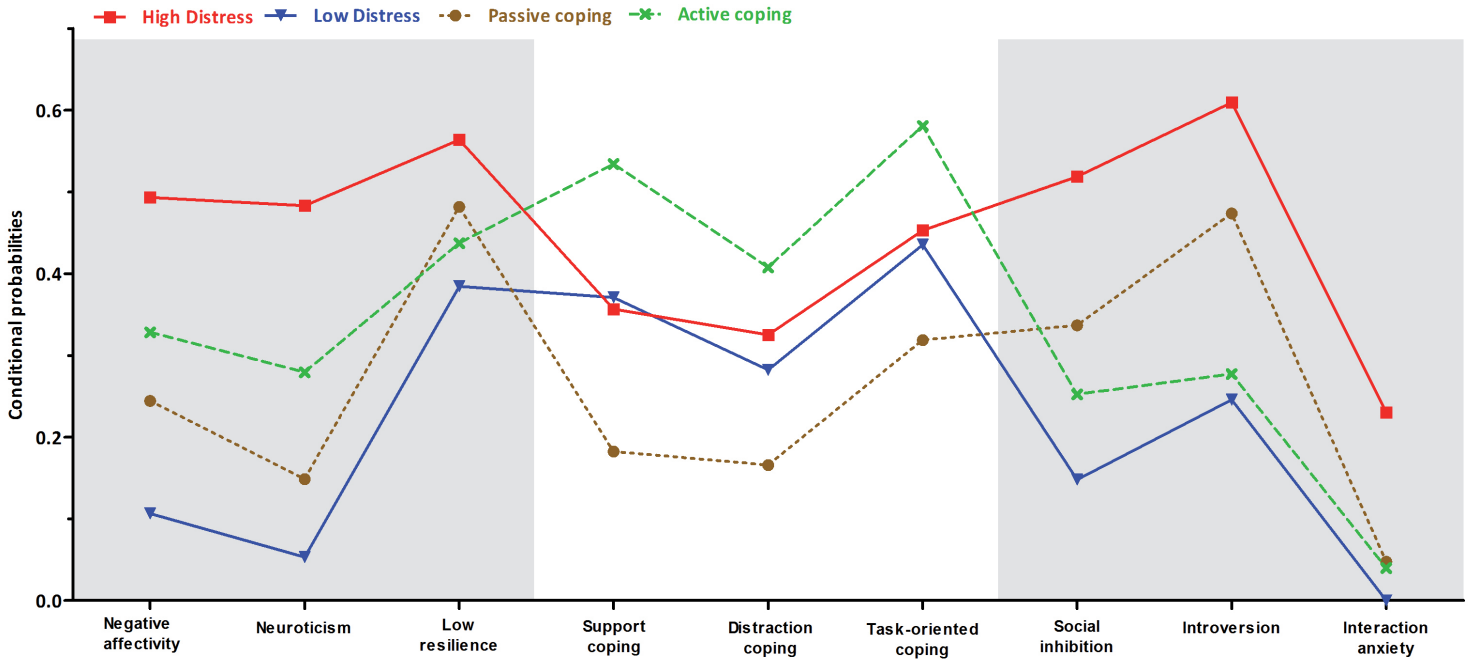

Figure 1. Personality profiles of patients with CAD.

Table 4. Demographic and clinical characteristics of personality profiles

	Low distress (n=204)	Passive coping (n=138)	Active coping (n=131)	High distress (n=184)		
Psychological symptoms[1]	% (n)	% (n)	% (n)	% (n)		
Anxiety (GAD-7)*	3 (7)	6 (8)	9 (12)	30 (54)		
Depression (PHQ-9)*	3 (7)	6 (8)	12 (16)	26 (46)		
Type D personality (DS14)*	0 (0)	15 (19)	11 (15)	65 (117)		
Model 1. Demographics	Odds				Wald	p-value
Age	1	1.01	1.00	.98	3.73	.29
Women	1	1.09	1.52	1.54	3.18	.36
No partner	1_{a}	$.97_{b}$	$.91_{c}$	$2.89_{a,b,c}$	21.23	**.0001**
Work status					26.39	**.0001**
Unemployed	$1_{a,b}$	$.76_{c,e}$	$1.53_{b,d,e}$	$.62_{a,c,d}$		
Retired	$1_{a,b}$	$.86_{c,e}$	$.60_{b,d,e}$	$.37_{a,c,d}$		
Model 2. Clinical Characteristics	Odds				Wald	p-value
Acute PCI indication	1	.78	1.02	1.14	1.80	.61
Cardiac history[1]	1	1.03	.93	1.07	.30	.96
Comorbidities[2]	1_{a}	.65	$.48_{a}$	.63	7.83	*.05*
Hypercholesterolemia	1	1.30	1.02	1.36	2.29	.51
Hypertension	1	.91	1.16	1.07	.74	.86

GAD-7 = Generalized Anxiety Disorder Questionnaire 7, PHQ-9 = Patient Health Questionnaire 9, DS14 = Type D scale 14,

*recommended cut-off ≤10 was used

PCI = percutaneous coronary intervention; [1]previous myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting; [2]cerebrovascular accident, transient ischemic attack, peripheral arterial disease, chronic obstructive pulmonary disease, kidney disease, rheumatism, cancer, diabetes mellitus; $_{a-d}$ indicate significant differences between subgroups resulting from post-hoc analysis; Bold = p≤.05, Italic = p<.10.

sizes (Cohen's d) of the subgroups' scores on patient-reported outcomes in relation to the reference group.

Anxiety, depression, and negative mood (Figure 2a-c) – Compared to the other subgroups, patients with a High distress profile experienced the highest levels of anxiety, depression, and negative mood at six months follow-up (all d's >.94), while the lowest scores on these outcomes were observed in patients with a *Low distress* profile. Low scores for emotional problems were also observed in patients with a *Passive coping* profile, except for anxiety, which was significantly higher than in the *Low distress* group (all d's >.19). Patients with an *Active coping* profile reported significantly higher levels of emotional problems at follow-up than patients with a *Passive coping* profile (all d's >.50).

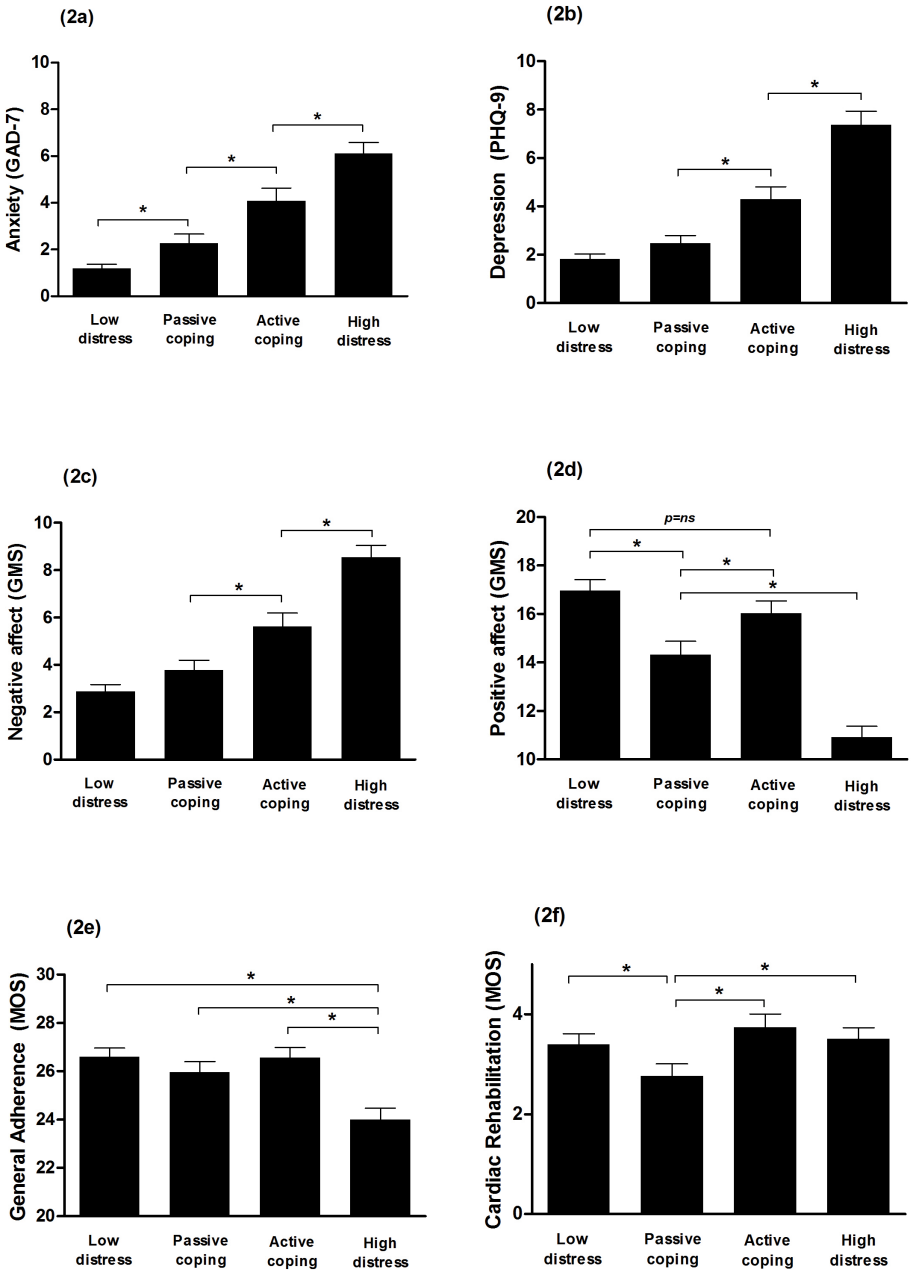

Figure 2. Association of personality profiles with patient-reported outcomes at six-months.
Note. GAD-7 = Generalized Anxiety Disorder Questionnaire 7, PHQ-9 = Patient Health Questionnaire 9, GMS = Global Mood Scale, MOS = Medical Outcomes Study Questionnaire.

Table 5. Effect sizes of the personality profiles in relation to the reference subgroup

	Passive coping (n=138)	Active coping (n=131)	High distress (n=184)
	Cohen's d		
Anxiety (GAD-7)	.30	**.59**	**.99**
Depression (PHQ-9)	.19	**.52**	**.94**
Negative mood (GMS)	.19	**.50**	**1.00**
Positive mood (GMS)	-.40	-.15	**-1.02**
General adherence (MOS)	-.12	-.01	**-2.75**
Cardiac rehabilitation (MOS)	.04	.13	.04

Note. GAD-7 = Generalized Anxiety Disorder Questionnaire 7, PHQ-9 = Patient Health Questionnaire 9, GMS = Global Mood Scale, MOS = Medical Outcomes Study Questionnaire; medium to large Cohen's d values are presented in bold.

Positive mood (Figure 2d) – There were also significant differences in positive mood between the four subgroups. The *Low distress* and the *Active coping* subgroups both reported highest levels of positive affect at follow-up (d=-.15). The lowest positive mood levels were observed in patients with a *High distress* profile (d=-1.02).

Adherence – Compared to the other subgroups, patients with a *High distress* profile reported significantly lower treatment adherence at follow-up (d=-2.75; Figure 2e). Differences in treatment adherence between the other subgroups were not significant (all d's <-.12). Compared to the other subgroups (which among themselves showed no differences), patients with a *Passive coping* profile participated less often in cardiac rehabilitation (all d's <.13; Figure 2f).

DISCUSSION

The current study aimed to explain heterogeneity in patient-reported outcomes of patients with CAD, based on a set of relatively stable individual differences in personality and coping styles. For this purpose, we applied a person-centered approach, capturing exploratory information that is immediately relevant to patient-reported outcomes following PCI. This approach revealed four personality profiles: *Low distress*, *High distress*, *Active coping*, and *Passive coping*, which were differentially characterized by marital status, work status, and the presence or absence of comorbid conditions. Importantly, these profiles were also significantly associated with differences in patient-reported outcomes at 6 month follow-up.

An exploratory factor analysis on multiple personality traits and coping styles, which was performed to create a framework for the person-centered latent class analysis, revealed

three underlying dimensions: negative affectivity, coping, and inhibition. The high loadings of the traits negative affectivity, neuroticism, and low resilience on the first dimension is in line with previous research showing a broad and general tendency to experience high levels of fear, sadness, distress, and physiological arousal (33, 34). Resilience, the ability to quickly adapt to a stressful event, demonstrated a strong negative relationship with negative affectivity and neuroticism (52). Emotion-focused coping, which is characterized by focusing on negative and distressing emotions that a stressful situation has caused (e.g. blame myself for procrastinating, worrying, getting upset) (53), loaded on the negative affectivity and coping dimension. The other three coping styles represent more active behaviors to deal with stressful situations and loaded on the second dimension. Finally, social inhibition, extraversion and social interaction anxiety loaded on the third dimension, inhibition. The overlap between these concepts has already demonstrated in previous studies (33), and is confirmed in this factor analysis.

The person-centered latent class analysis identified four latent subgroups. A first profile consisted of patients with a *Low distress* profile, characterized by low levels of negative affectivity and inhibition, and a moderate coping level. Patients with this profile experienced the lowest levels of anxiety, depression, and negative mood and highest levels of positive mood at six months follow-up. Patients with this profile were more often retired as compared to the other profiles. They were also more often in a relationship than patients in the *High distress* subgroup. This is in line with previous research showing that married retirees enjoy better psychological well-being than single or widowed retirees (54).

In contrast, patients with a *High distress* profile were characterized by high levels of both negative affectivity and inhibition. Similar to the *Low distress* group, they scored moderately on the coping dimension. Compared to the other subgroups, these patients experienced the highest level of anxiety, depression, and negative mood, and the lowest level of positive mood, six months after their PCI treatment. They also showed poor treatment adherence (general and cardiac rehabilitation) at follow-up. Importantly, patients with a *High distress* profile are characterized by the prototypical Type D profile (combination of high negative affectivity and high social inhibition), which has previously been associated with emotional problems, poor treatment adherence, adverse cardiac events and mortality (19, 33, 55-57). Moreover, patients with this profile were more often single and employed. This may be considered an example of intercorrelation between risk-factors that reflect individual characteristics (e.g. Type D personality) and those that reflect the social environment (e.g. social isolation, conflict) (58). The combination of Type D personality, being single, and being employed might be a more accurate predictor of emotional symptoms at follow-up than a single psychosocial factor (58).

The third subgroup comprised patients with an *Active coping* profile, which was determined by increased negative affectivity and low inhibition. This profile was also

characterized by high levels of seeking social support, distraction coping, and task-oriented coping. At follow-up, these patients reported both increased levels of emotional symptoms and of positive mood. Compared to the other subgroups, patients with an *Active coping* profile may be characterized by having an increased awareness of their own mental state regarding both positive and negative emotions. In earlier work we already described the co-occurrence of positive and negative feelings and accentuated that positive and negative psychological constructs should not be considered opposites of one continuum, but rather should be interpreted as two independent and uncorrelated dimensions (59). Also, the fact that higher levels of both positive and negative states are observed at follow-up may partially be explained by the co-occurrence of different coping styles within this profile, i.e. both distraction coping and task-oriented coping. Previous work showed an association between distraction coping and poorer psychological outcomes, while task-oriented coping was associated with more adaptive outcomes (60). Moreover, patients with this profile were more often unemployed than patients in the other subgroups, which may contribute to the higher levels of emotional problems at follow-up (61).

Finally, the *Passive coping* profile was defined by low levels of active coping, increased introversion, and low negative affectivity. Patients with this profile did not seem to suffer from emotional problems at follow-up. However, participation to cardiac rehabilitation was significantly lower in these patients, which might be explained by the fact that they have the tendency to take a passive stance (53), and they displayed a decreased level of positive mood. Furthermore, patients with this profile more often had a partner than patients with a *High distress* profile and were more often retired than patients with an *Active coping* and *High distress* profile. The combination of being married and being retired may partly explain the decreased risk for emotional problems at follow-up (54).

Our data showed important differences between the four profiles that may help to explain the large degree of heterogeneity in outcomes at six months following PCI. Patient-reported outcomes seem to be the result of a combination of emotional distress levels, other psychosocial characteristics, as well as how a patient copes with the stress associated with the cardiac event. Remarkably, within each profile, levels for all three coping styles (social support, distraction, and task-oriented coping) were all high, all low, or all moderate, and were therefore interpreted in terms of active vs. passive. However, we are not able to unequivocally classify the identified profiles in terms of adaptive and maladaptive mechanisms, because adaptiveness is dependent upon the situational context, and outcome measure used. Patients with a *Passive coping* profile show low levels of emotional symptoms at follow-up. Therefore, in a certain way, passive coping seems to be adaptive. However, treatment adherence was poor in these patients, which can be considered maladaptive. Patients with a *Passive coping* profile may thus benefit emotionally from their passive stance in the short term, but in the long term their poor treatment adherence may adversely affect their

disease prognosis. In contrast, the *Active coping* profile was associated with high levels of (positive and negative) emotional symptoms, but also high treatment adherence at follow-up. Consequently, increased levels of emotional symptoms may be interpreted as evidence of the body's healthy efforts to cope with the cardiac event, reflecting the brain's homeostatic effort to cope with sudden changes in the body's internal and external environment (25). In these patients, the increased levels of emotional symptoms may function as a trigger that positively affects patients' motivation to deal with the cardiac event, e.g. by learning to adjust their lifestyle during cardiac rehabilitation or by following their cardiologist's treatment advice.

These inter-individual differences are useful for further scientific research. Considering patients' personality profiles in addition to single characteristics, might add important explanatory and predictive power. Moreover, our results are helpful in personalized medicine, which aims to individualize care according to the patients' unique characteristics (30-32). More individualized solutions might be considered for CAD patients. Besides focusing on psychological symptoms such as depression and anxiety, positive psychological functioning (i.e. increased positive mood or patients' coping styles) may be a useful target for intervention. While the choice of coping strategies often is involuntary, application of ways of coping can be trained, reflecting a more voluntary choice process (25). Strengthening patients' resources may improve well-being, treatment adherence, and cardiac rehabilitation adherence (10). Moreover, positive psychological functioning could moderate the deleterious effects of emotional problems, such as depressive symptoms, on adherence behavior (62). Furthermore, for specific subgroups of patients, for example these with a *Passive coping* profile, special attention for the enrolment for cardiac rehabilitation may be offered, because they are less prone to actively deal with stressful events and associated emotions (53).

These results should be viewed in light of its strengths and limitations. Key strength of the present study is its clearly defined and relatively large patient population, representing an important part of the real-world population of patients with CAD. Multiple independent (e.g. negative affectivity and resilience) and dependent (e.g. adherence and depression) measures were included. However, the dependent variables only included patient-reported outcomes at a relatively short follow-up period. In the current sample, it was impossible to examine the association between the profiles and cardiac events at six months, because the event prevalence was <2%. This is in line with recent findings showing that six month mortality after myocardial infarction has decreased considerably over the past two decades (63). However, for a further determination of heterogeneity in the prognosis of patients with CAD, it may be interesting to look beyond six-month outcomes and examine the association between the profiles with longer term and other clinical outcomes. Furthermore, all personality and coping characteristics were assessed with self-report instruments, which may not completely reflect actual psychological functioning and behaviors.

In conclusion, the current study highlights the advantage of studying heterogeneity in CAD patients from a person-centered perspective. The four different identified personality profiles, reflecting specific combinations of multiple personality traits, coping styles, and other psychosocial characteristics may be more accurate predictors of patient-reported outcomes than a single psychosocial factor. Six months after the PCI treatment, highest levels of emotional distress and lowest levels of positive mood and treatment adherence were observed in patients with a *High distress* profile. The *Active coping* profile was also associated with increased emotional distress at follow-up, but also with adequate positive mood and participation to cardiac rehabilitation was relatively high. Patients with a *Low distress* or *Passive coping* profile seem to experience relatively little psychological symptoms at follow-up. However, the *Passive coping* profile was associated with decreased participation in cardiac rehabilitation and decreased positive mood. These results are useful in explaining heterogeneity in the clinical course of CAD patients, but also for personalized medicine. Future research should examine the association between subgroup membership with longer term patient-reported and other clinical outcomes.

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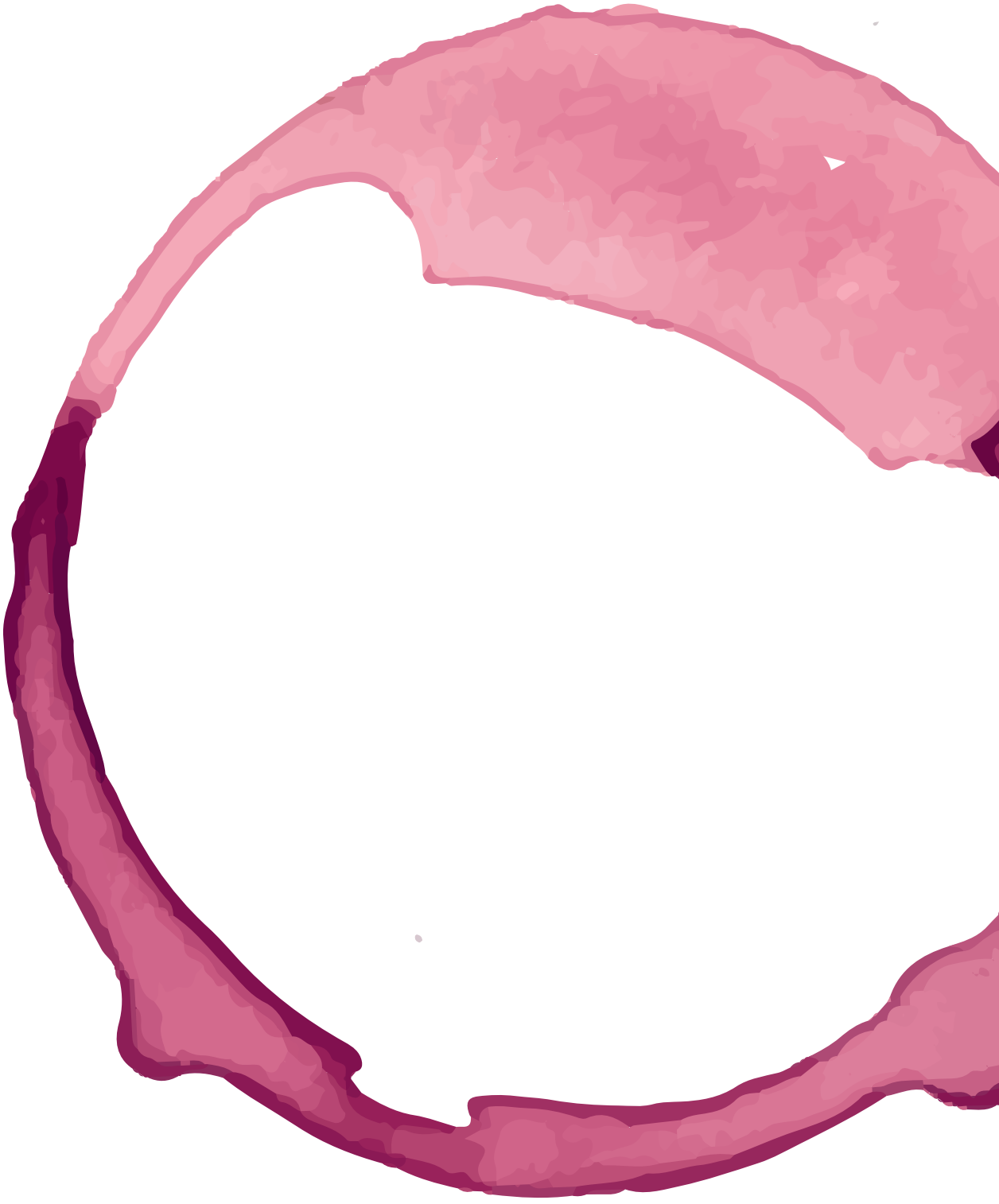

Chapter 5

Interrelation and independence of positive and negative psychological constructs in predicting general treatment adherence in coronary artery patients – results from the THORESCI study

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ABSTRACT

Background: In cardiac patients, positive psychological factors have been associated with improved medical and psychological outcomes. The current study examined the interrelation between and independence of multiple positive and negative psychological constructs. Furthermore, the potential added predictive value of positive psychological functioning regarding the prediction of patients' treatment adherence and participation to cardiac rehabilitation (CR) was investigated.

Method: 409 percutaneous coronary intervention (PCI) patients were included (mean age=65.6 ± 9.5; 78% male). Self-report questionnaires were administered one month post-PCI. Positive psychological constructs included positive affect (GMS) and optimism (LOT-R); negative constructs were depression (PHQ-9, BDI), anxiety (GAD-7) and negative affect (GMS). Six months post-PCI self-reported general adherence (MOS) and CR participation were determined.

Results: Factor Analysis (Oblimin rotation) revealed two components (r=-.56), reflecting positive and negative psychological constructs. Linear regression analyses showed that in unadjusted analyses both optimism and positive affect were associated with better general treatment adherence at six months ($p<.05$). In adjusted analyses, optimism's predictive values remained, independent of sex, age, PCI indication, depression and anxiety. Univariate logistic regression analysis showed that in patients with a cardiac history, positive affect was significantly associated with CR participation. After controlling for multiple covariates, this relation was no longer significant.

Conclusions: Positive and negative constructs should be considered as two distinct dimensions. Positive psychological constructs (i.e. optimism) may be of incremental value to negative psychological constructs in predicting patients' treatment adherence. A more complete view of a patients' psychological functioning will open new avenues for treatment. Additional research is needed to investigate the relationship between positive psychological factors and other cardiac outcomes, such as cardiac events and mortality.

INTRODUCTION

Psychological risk factors play a substantial role in cardiac outcomes (1). Both depression and anxiety are associated with development of cardiovascular diseases (CVD) (2, 3). Moreover, depression is considered a prognostic risk factor in patients with acute coronary syndrome (4). Other detrimental psychological factors, such as perceived stress (5), hostility (6) and Type D personality (7) may also have a negative influence on incidence and course of multiple cardiovascular conditions and may act through several distinct psychobiological mechanisms that are directly involved in the pathogenesis of CVD (8).

Whereas past research has predominantly focused on the relationship between poor psychological functioning and cardiovascular health, more recent studies suggest cardiovascular health also to be related to positive psychological functioning (9-11). Examples of such constructs are *Optimism*, which reflects the dispositional tendency to believe that good things will happen and to attribute causes of past events favorably (12), and *Positive affect* which refers to pleasant and activated mood states (e.g. happy, active) (13). Both have been shown to predict an improved overall health status, better cardiac outcomes and reduced risk of cardiac mortality (9-11, 14-16) independent of medical illness severity. However, other studies show contrasting findings, e.g. in stroke patients optimism was not associated with disease severity, recurrence or mortality (17).

However, former studies have mainly focused on individual psychological concepts, and knowledge about interrelations between and interactions of multiple negative and positive psychological constructs in heart patients is still lacking (9-11). Where earlier research considered negative and positive psychological functioning as opposite ends of a continuum, suggesting that what was known about psychological distress was also applicable for positive psychological functioning (18), more recent research seems to support an "independence perspective". This new perspective presumes negative and positive psychological functioning to be separate, independent dimensions of mental health (18). Although there may be some inverse correlation between particular positive and negative constructs, e.g. depression and optimism (19), absence of depression does not necessarily imply high positive affect, or optimism (9, 14-16, 18). Additionally, psychological distress and positive psychological functioning have different biological and neural correlates (18, 20), and in clinical situations, e.g., in long-term treatment of recurrent depression, promoting adequate positive psychosocial resources and reducing negative cognitions are considered separate treatment methods that are both needed (18).

In addition to the need for knowledge about interrelationships between and interactions of multiple negative and positive psychological constructs, more research about positive psychological constructs regarding prediction of cardiovascular outcomes is required (21). It is for example unclear whether cardiac outcomes are more or less related to specific

(clusters of) positive constructs, or whether all positive constructs should be considered one overall predictive factor (21). Moreover, there is consistent evidence about constructs that may play a role in this relationship, for example about specific health behaviors including diet and exercise, which may be points of action during cardiac rehabilitation (21, 22). However, other modifiable health behaviors such as "adherence" (the degree to which a patient's behavior matches recommendations from a physician), which is a predictor of cardiovascular prognosis in the months following a cardiac event (23-25), might also be important in this relationship (e.g. as an intermediate outcome). Examining the relationship between positive psychological constructs and adherence might help building the theoretical framework explaining pathways between positive psychological functioning and cardiovascular outcomes. Besides, for clinical practice, understanding of the role of positive psychological well-being might provide new ways for intervention and help in designing tailor-made programs promoting a healthy lifestyle, e.g. a positive psychology intervention such as the online positive affect skills intervention (26-28).

Therefore, in the current study, the main aim was to investigate the interrelations between and independence of multiple positive (optimism, positive affect) and negative (anxiety, depression, negative affect) psychological constructs in a real-world cardiac population to explore the underlying structure. We also investigated whether the assessment of positive psychological factors is of incremental value to negative psychological functioning, regarding the prediction of treatment adherence and participation to cardiac rehabilitation.

METHODS

Patient population and procedure – the THORESCI study

The current study was part of a large prospective and ongoing observational cohort study, the "**T**ilburg **H**ealth **O**utcomes **R**egistry of **E**motional **S**tress after **C**oronary **I**ntervention (THORESCI)", which recruits participants from the clinical standard of care Percutaneous Coronary Intervention (PCI) Registry at the Elisabeth-TweeSteden Hospital in Tilburg, the Netherlands. All patients who were scheduled for either elective or acute PCI for 1 or more coronary occlusions were included. Patients had to be over 18 and needed to have sufficient understanding of the Dutch language to fill out questionnaires. Sufferers from life-threatening comorbidities (e.g., metastasized cancer) or cognitive disorders were excluded. On the day of the PCI, patients were approached by a member of the research team who explained the study content and its requirements. After providing written consent, the patients were asked to fill out a set of validated psychosocial questionnaires at several moments post-PCI. For the current study, only data from baseline (within one week post PCI), from one month

post PCI and from six months post PCI were used. All self-report questionnaires concerning emotional distress and positive psychological functioning were conducted one month after PCI. Furthermore, complete medical records were obtained. The study protocol is in line with the Helsinki declaration and was approved by the institutional medical ethics review board.

Emotional distress

Depression – One of the two instruments used to assess symptoms of depression was the reliable and valid Patient Health Questionnaire (PHQ-9) (29). This measure consists of 9 items (e.g., "Little interest or pleasure in doing things"), based on the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria of depression. Items are rated on a Likert scale from 0 ("not at all") to 3 ("almost every day") (29). For major depressive disorder the recommended cut-off score is ≥10 (29). In the present study, the internal consistency of the PHQ-9 at baseline was high (Cronbach alpha at .85). The second instrument to determine depression symptoms was the 21-item Beck's Depression Inventory (BDI). Cognitive and somatic items are rated on a Likert scale from 0 ("no depressive complaint") to 3 ("severe depressive complaint") (30). The following cut-off scores are advised: <10 = no or minimal depression, 10-18 = mild to moderate depression, 19-29 = moderate to severe depression and 30-63 = severe depression (30). In the present study, this questionnaire had high internal consistency (Cronbach alpha at .84).

Negative affect – Negative affect was assessed using the Global Mood Scale (GMS). This instrument comprises two subscales. For negative affect only the 10 negative affect terms (e.g., "fatigued" and "listless") were used (13). Items are rated on a five-point Likert scale from 0 "not at all" to 4 "extremely". In the current study this scale had high internal consistency (Cronbach alpha at .89).

Anxiety – Anxiety symptoms were estimated using the Generalized Anxiety Disorder (GAD-7) scale, a valid and efficient tool to screen for generalized anxiety (31). The seven items are scored on a Likert scale form 0 ("not at all"), to 3 ("almost every day") (31). The recommended cut-off score is ≥10 (31). In the current study, internal consistency was excellent (Cronbach alpha = .91).

Positive psychological functioning

Optimism – The Revised Life Orientation Test (LOT-R) was used to assess optimism. This questionnaire consists of ten statements, of which three are worded positively (e.g. "In uncertain times, I usually expect the best") and three negatively (e.g. "If something can go wrong, it will"). For the current study, we used all six items to create the LOT-R total score (range: 0-30), which we will call optimism throughout. The other 4 items are "filler" items.

All items are rated on a 5 point Likert scale from 0 "I disagree a lot" to 5 "I agree a lot" (32). Cronbach alpha for the optimism scale was .72.

Positive affect – Positive affect was assessed using the Global Mood Scale (GMS). This instrument comprises two subscales. For positive affect only the ten positive affect terms ("lively" and "bright") were used (13). Items are rated on a five-point Likert scale from 0 "not at all" to 4 "extremely". In the current study this scale had high internal consistency (Cronbach alpha at .87).

Treatment adherence

Self-reported general treatment adherence – Self-reported treatment adherence was assessed at 6 months post-PCI using the first part of the Medical Outcomes Study (MOS) questionnaire (33). This scale comprises 5 items concerning general treatment adherence (e.g. "I followed my doctor's suggestions exactly") which are rated on a 6-point Likert scale from 1 "never" to 6 "always". In the present study, this scale had adequate internal consistency (Cronbach alpha = .72).

Cardiac rehabilitation participation – An objective measure of treatment adherence was extracted from patients' medical records, containing information about Cardiac Rehabilitation (CR). In the Elisabeth-TweeSteden Hospital Tilburg, CR is an 8-week medically supervised program, including exercise training, education on heart healthy living and psychosocial support. Some PCI-patients lack a medical CR record, e.g. because they wanted to attend to an external CR program (e.g. personal physiotherapist) or refused entirely. A minority of patients subscribed to an external CR program. For these patients, we retrieved information on the location and type of CR and their starting date from the 6-month follow-up questionnaire. In total, a dichotomous variable was constructed in with 0 indicated "not started with CR" and 1 indicated "started with CR".

Other variables

Demographic and medical variables were obtained from self-report questionnaires and patients' medical records at baseline and included sex, age, cardiac history (previous myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, and/or myocardial infarction), risk factors (family history of heart disease <60 years, hypercholesterolemia and diabetes mellitus type 2) and PCI indication (acute vs. elective).

Statistical analyses

To determine the latent structure of multiple negative and positive psychological constructs, explorative factor analyses, using the principal axis factoring method with Oblimin rotations was used. This is a method to condense multiple total scores to a smaller, more manageable number of dimensions or factors (34). Catell's scree test and Eigenvalues (>1.0) (34) were calculated to aid in determining the number of factors.

Furthermore, to examine the relationship between positive psychological factors and self-reported adherence univariate analyses, unadjusted and adjusted hierarchical multivariable regression analyses were performed. In step 1, positive psychological constructs (optimism and positive affect) were entered (*unadjusted* model). In step 2, the model was adjusted for demographic (sex, age) and medical (cardiac history, PCI indication) covariates. In step 3, depression and anxiety were added to the model. To examine the relationship between positive psychological factors and participation to CR, unadjusted and adjusted logistic regression analysis were performed. Patients with and without a cardiac history were analyzed separately, because patients who already experienced cardiac events in the past may also have had earlier opportunities to participate in CR, and may behave differently for that reason. The assumption of multicollinearity was checked for all separate multivariable linear regression models. All statistical analyses were performed using SPSS 22 (IBM SPSS Statistics for Windows, Version 22. Armonk, NY: IBM Corp USA). A p-value of $p<.05$ was considered significant.

RESULTS

Sample characteristics

The current paper concerns those participants recruited for THORESCI between December 2013 and April 2015. Of those who were eligible (643; 85%), 455 (71%) were included (mean age=64.7±11.8; 78% male). Of those, at the time of data extraction, 409 patients had filled out the one-month follow-up questionnaire and these were included in the Factor Analysis and 328 also produced follow-up data at six months. Most common reasons for refusal to participation were: (a) feeling too sick or tired to fill out the questionnaire packets; or (b) being uninterested in participating in research of any kind. Baseline characteristics and the number of patients with a total score on depression, anxiety, positive and negative affect, optimism and adherence are presented in Table 1. For general treatment adherence (MOS) six months after the PCI mean score was 25.6, SD=4.6. A total of 65% (266) of the patients started CR.

Table 1. Baseline Patient Characteristics and total scores for questionnaires (n=409)

Demographics	N	%
Men	319	78
Age	65.6 (SD=9.5)	-
Medical	**N**	**%**
Cardiac history[1]	191	48
Risk factors[a]		
Family history	162	41
Hypercholesterolemia	144	36
Diabetes Mellitus Type 2	48	12
PCI indication[b]		
Acute	274	69
Elective	125	31
Total scores for questionnaires, one month after PCI (n=397-409)[c]	**Mean**	**SD**
Depression (PHQ-9)	3.6	4.3
Depression (BDI)	9.2	6.6
Anxiety (GAD-7)	3.1	4.0
Positive affect (GMS)	14.1	5.4
Negative affect (GMS)	5.3	4.7
Optimism (LOT-R)	14.5	4.0
Adherence (MOS), six months after PCI (n=328)	25.7	4.5
CR participation	266	65

PCI = percutaneous coronary intervention, CR = Cardiac Rehabilitation; [1]previous myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting; Missing values: [a]incomplete medical records = 12 (3%); [b]incomplete medical records = 10 (2%); [c]some acute patients failed to fully complete questionnaire due to stressful coronary event and/or length survey.

Factor Analysis of multiple psychological constructs

To determine the underlying structure of positive and negative psychological constructs, total scores of the psychological constructs were subjected to principal component analysis. First the suitability of the data for factor analysis was assessed. Inspection of the correlation matrix revealed the presence of many coefficients of .35 and above (Table 2). The Kaiser-Meyer-Olkin value was .9, exceeding the recommended value of .6 and the Barlett's Test of Sphericity (35, 36) reached statistical significance, supporting the factorability of the correlation matrix. Factor analysis revealed the presence of one component with an eigenvalue exceeding 1 (Table 2). The scree plot (37) showed a break (elbow) around the second component (Figure 1). Oblimin rotation with two fixed factors was performed to aid in the interpretation and revealed two components showing a number of strong factor loadings. The factors were correlated moderately, at -.56. The first component represents *negative psychological*

constructs, involving total scores of depression (BDI and PHQ-9), anxiety (GAD-7) and negative affect (GMS). Component 2, *positive psychological constructs*, involves optimism (LOT-R) and positive affect (GMS). Rotated factor loadings and cross loadings are listed in Table 2.

Table 2. Summary of exploratory factor analysis results for multiple positive and negative psychological constructs

	Correlation matrix						Rotated factor loadings	
Items	1.	2.	3.	4.	5.	6.	Negative constructs	Positive constructs
1. Depression (PHQ-9)	1.00						.94	-.50
2. Anxiety (GAD-7)	.79	1.00					.88	-.44
3. Negative affect (GMS)	.71	.60	1.00				.87	-.53
4. Depression (BDI)	.78	.67	.64	1.00			.83	-.50
5. Optimism (LOT-R)	-.42	-.40	-.36	-.47	1.00		-.45	.88
6. Positive affect (GMS)	-.47	-.41	-.50	-.44	.48	1.00	-.52	.84
Eigenvalue							3.75	.83

PHQ-9= Patient Health Questionnaire 9, GAD-7= Generalized Anxiety disorder 7, GMS= Global Mood Scale 12, BDI= Beck Depression Inventory, LOT-R= Life Orientation Test Revised.

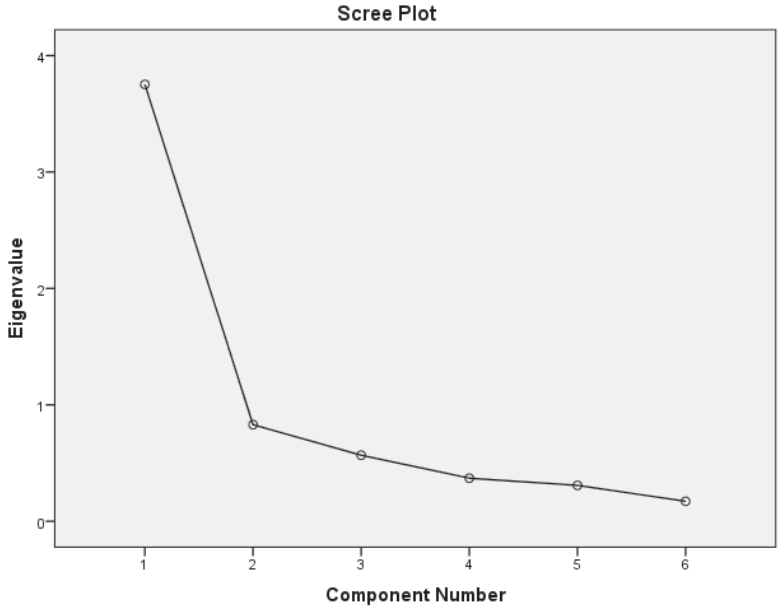

Figure 1. Scree plot for Exploratory Factor Analysis on multiple positive and negative psychological constructs.

Association of multiple positive psychological constructs with 6–month patient–reported general treatment adherence

Univariate regression analysis were conducted to examine the relationship between positive psychological predictors (optimism and positive affect) and general treatment adherence. Univariate linear regression analysis showed that both optimism (β=.28, p<.001, adj. R^2=.08)

Table 3. Multivariable regression models of self-reported adherence

	Self-reported General treatment adherence			
	B	SE B	β	p-value
Step 1. Unadjusted model				
Optimism	.25	.07	.22	**.001**
Positive affect	.10	.05	.11	*.069*
R^2=.09 , Adjusted R^2=.08, ΔR^2=.09, p<.001				
Step 2. Covariates adjusted model				
Optimism	.32	.07	.28	**.0001**
Age	-.06	.03	-.13	**.034**
Female sex	-.74	.64	-.07	.249
Cardiac history[1]	.20	.57	.02	.727
PCI indication - acute	-.04	.32	-.01	.903
R^2=.12 , Adjusted R^2=.10, ΔR^2=.12, p<.001				
Step 3. Complete model (covariate adjusted + baseline depression)				
Optimism	.28	.08	.23	**.0001**
Age	-.07	.03	-.13	**.019**
Female sex	-71	.70	-.15	.271
Cardiac history[1]	.27	.57	.02	.643
PCI indication - acute	-.12	.31	.01	.960
Depression (PHQ-9)	-.1	.07	-.08	.139
R^2=.12 , Adjusted R^2 = .10, ΔR^2=.12, p<.001				
Step 4 Complete model (covariate adjusted + baseline anxiety)				
Optimism	.26	.07	.23	**.0001**
Age	-.07	.03	-.16	**.010**
Female sex	-.71	.64	-.07	.264
Cardiac history[1]	.31	.56	.03	.586
PCI indication - acute	-.02	.32	-.00	.955
Anxiety (GAD-7)	-.16	.07	-.16	**.014**
R^2=.14 , Adjusted R^2=.12, ΔR^2=.14, p<.001				

p-values <.05 are listed in bold, trend values (p<.10) are printed in italic; [1] previous myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, myocardial infarction. PCI indication = (sub)acute vs. elective; PHQ-9 = Patient Health Questionnaire 9, GAD-7 = Generalized Anxiety disorder 7.

and positive affect (β=.22, p<.001, adj. R^2=.05) were positively and significantly correlated with treatment adherence, indicating that those with higher scores on these two variables tend to have higher 6-month general treatment adherence.

After the univariate analyses, multiple hierarchical multivariable linear regression analyses were conducted. In all multivariable linear regression models, the assumption of non-multicollinearity was met. The multivariable regression model with a combination of both positive predictors (optimism and positive affect) produced adj. R^2=.08, p<.001. As can be observed from Table 3, in this model, only optimism had significant positive regression weights, indicating patients with higher optimism scores showed better 6 month general adherence. Optimism was still significantly related with better 6 months treatment adherence after controlling for demographic variables (age and sex) and medical variables (cardiac history and PCI indication). In two separate final models, we then added depression and anxiety, with results showing higher optimism at baseline to be associated with better patient-reported general treatment adherence at 6-months follow-up, independent of depression and anxiety (Table 3).

Association of positive psychological constructs with cardiac rehabilitation participation

There was a significant effect of history of cardiac disease, as expected. Univariate logistic regression analysis showed that in patients with a history of cardiac disease, positive affect was significantly correlated with participation to Cardiac Rehabilitation (OR=.94, 95% CI: .89-.99, p=.04). This indicates that those patients with higher positive affect scores tend to have lower CR participation rates. After controlling for demographic variables (age and sex) and PCI indication, positive affect was no longer significantly associated with starting CR (Table 4). Optimism was not significantly associated with CR participation (OR=.97 95% CI: .88-1.01. p=.139). Mirroring the analysis of the subjective general adherence outcome, we then added depression and anxiety, with results showing no significant association of positive affect, depression or anxiety with objective participation to CR (Table 4).

In patients without a history of cardiac disease, optimism, positive affect (or negative affect) were not significantly associated with CR participation. In the total sample, without considering cardiac history, none of the positive psychological factors was associated with starting CR.

Table 4. Logistic regression models of cardiac rehabilitation participation

	Cardiac Rehabilitation participation					
	History of cardiac diseases			No history of cardiac diseases		
	OR	95% CI	p-value	OR	95% CI	p-value
Step 1. Unadjusted model						
Positive affect	.94	.89-.99	**.036**	1.01	.95-1.07	.873
Step 2. Covariates adjusted model						
Positive affect	.97	.90-1.04	.324	1.02	.94-1.1	.707
Age	.97	.92-1.02	.202	.96	.92-1.01	.085
Female sex	.98	.36-2.67	.975	.99	.34-2.90	.990
PCI indication – acute	1.01	.72-1.69	.666	.65	.41-1.05	*.076*
Step 3. Complete model (covariate adjusted + baseline depression)						
Positive affect	.99	.91-1.08	.892	1.03	.93-1.13	.606
Age	.97	.92-1.02	.240	.96	.91-1.01	.139
Female sex	.52	.17-1.57	.247	.84	.25-2.85	.781
PCI indication – acute	.92	.57-1.48	.740	.51	.29-.88	**.016**
Depression (PHQ-9)	1.07	.95-1.19	.258	1.04	.91-1.21	.523
Step 4. Complete model (covariate adjusted + baseline anxiety)						
Positive affect	.98	.91-1.06	.678	1.00	.91-1.11	.880
Age	.98	.92-1.03	.425	.96	.91-1.01	.119
Female sex	.89	.28-2.80	.422	.86	.26-2.88	.802
PCI indication – acute	.93	.58-1.49	.707	.51	.30-.89	**.017**
Anxiety (GAD-7)	1.08	.97-1.21	.150	.98	.87-1.1	.731

p-values <.05 are listed in bold, trend values (p<.10) are printed in italic; [1]previous myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, myocardial infarction PCI indication = (sub)acute vs. elective, PHQ-9 = Patient Health Questionnaire 9, GAD-7 = Generalized Anxiety disorder 7.

DISCUSSION

The aim of this prospective study was to report on interrelations between and independence of multiple positive and negative psychological constructs in a real-world cardiac population. Regarding the prediction of self-reported treatment adherence and participation to cardiac rehabilitation, this study investigated whether assessment of positive psychological functioning is of incremental value to the assessment of negative psychological functioning. Results demonstrated that negative psychological constructs (depression, anxiety, negative affect) and positive psychological constructs (positive affect and optimism) should not be considered opposites of one continuum, but rather should be interpreted as part of two distinct latent dimensions underlying these concepts. Second, we found that in

predicting general treatment adherence, optimism was of incremental value to the negative psychological constructs (depression and anxiety). Furthermore, in patients with a cardiac history and higher positive affect after PCI, lower CR participation rates were observed. However, after controlling for multiple covariates, this association was no longer significant.

Considering multiple negative and positive psychological constructs, the current factor analysis indicated the presence of two underlying components. The first component, *negative psychological constructs*, was composed of measures of depression, anxiety and negative affect. This supports previous findings that show high comorbidity between depression and anxiety (38). Negative affect is considered a general factor of subjective distress, and comprises a broad range of negative mood states, including fear, anxiety, sadness and loneliness (39). Component 2, *positive psychological constructs*, comprised positive affect and optimism. Both positive affect (the extent to which individuals experience pleasurable feelings) and optimism (dispositional tendency to believe that good things will happen) are part of the broader category of positive psychological well-being (12, 40, 41).

This basic two-dimensional structure can be demonstrated across all major lines of research on *affective structure* (self-rated affect, studies of mood words, and analyses of facial expressions) (42). Positive and Negative Affect are viewed as the more *higher-order* dimensions, because these two constructs represent the major dimensions of emotional experience (42). This perspective considers Positive Affect and Negative Affect as two major *independent* and *uncorrelated* bipolar dimensions (42). Also, the "independence perspective", which describes the broader and "overall psychological functioning" presumes Negative and Positive psychological functioning to be separate, independent dimensions of mental health (18). Yet, the current study reported the presence of two separate factors, but they were moderately correlated. Thus, the current findings are not completely in line with the earlier basic two-dimensional structure, but possibly this can be explained by the fact that the current study included a combination of information about psychological affective *states* ("how patients *recently* felt"; i.e. anxiety, depression, positive/negative affect) and *traits* (a more general affective tone (i.e. *optimism*).

It seems obvious that also in the current sample (coronary artery disease patients) a two-factor structure was found. In particular, this stable and robust two-dimensional configuration has been consistently identified across different research lines and populations, and also in a variety of countries (e.g., Sweden, Japan, China) (42). Consequently, the present research results aid in the interpretation of the complex mechanisms regarding the determinants predicting cardiovascular outcomes. Actually, it seems that also in coronary artery disease patients it is of major importance to highlight both positive and negative psychological functioning. This is in line with the patient-centered *Cumulative Complexity Model*, according to which outcomes can be affected by a combination of *patient capacity* and *patients' workload of demands* (43). The model highlights that *patient capacity*

comprises both patients' resources (e.g., psychological well-being) and patients' limitations (e.g., psychological complaints) (43). Accordingly, increasing positive affect and optimism could enhance patients' capacity, which should in turn induce better self-care (e.g., better treatment adherence) (43).

As a proof of principle, the current study sought to examine the relation between positive constructs and self-care (general treatment adherence and CR participation rate). Results showed that higher optimism predicted better general treatment adherence at 6-months follow-up, independent of covariates and depression and anxiety. This finding suggests that indeed optimism is improving patients' capacity to self-care and is in line with previous work showing positive psychological functioning to be related with an improved overall health status and better cardiac outcomes such as fewer re-hospitalizations, lower rates of cardiac events and lower mortality (9, 14-16). This relation was also found in other populations. In primary care patients for example, optimism was associated with active treatment adherence and in hypertension patients an association was found between emotional well-being and general adherence (diet, exercise, smoking status) (25, 44). Likewise, in an HIV patient group, optimism was associated with a more positive attitude toward medication taking (45). However, there have been negative findings too. In cardiac rehabilitation patients for example, no relation between optimism and adherence to the cardiac rehabilitation program was found (46). Though, this finding might be explained by the small sample size (n=46).

A possible explanation for the association between optimism and better treatment adherence is that patients with greater psychological well-being might use more adaptive coping strategies. Highly optimistic patients tend to easier engage in health behaviors that are advantageous for cardiovascular prognosis (e.g., exercising, eating healthy, avoiding smoking) (47). Another explanation is that optimism weakens associations between illness burden and psychological complaints (e.g., anxiety) (48).

However, for CR participation, the current study showed different results. Optimism was not significantly associated with CR participation. Lower CR participation rates were observed in patients with a cardiac history and higher positive affect after PCI. However, after controlling for multiple covariates, this association was no longer significant. In other studies, also lower CR participation rates among patients with cardiac history (e.g. previous PCI) were observed (49). Earlier participation to CR (making patients more or less motivated to start again) or patients' cardiac self-efficacy (a person's belief in his/her ability to manage the challenges posed by a coronary disease (50)) may play a role in this relationship (51). In addition, the interaction of the patient with intake-nurse may be different in a patient displaying positive affect, as compared to patients displaying negative emotions, which might result in differences in the level of influence the nurse's arguments have on the willingness to participate. Psychological research suggests that in a positive mood, people rely more on

scripted behavior patterns, while negative affective states may warn a person that a situation may be problematic, paying more attention to details, and may result in the patient being influenced more by the nurse's arguments (52). However, future work in this area is needed.

The difference in the association of positive and negative psychological constructs with self-reported adherence versus more objective measures of adherence is in line with previous research. I.e. a recent meta-analysis showed that while depression was associated with subjective self-care in heart failure patients, it was not associated with objective measures of self-care (53).

For clinical practice, positive psychological functioning (i.e., optimism and positive affect) might be a useful target for intervention. The current results imply that besides *treatment of complaints* (e.g. depression treatment by a medical psychologist), it might also by appropriate to *strengthen patients' resources*, e.g. increasing optimism and/or positive affect with gratitude exercises and kindness interventions (26, 47, 54). Promoting positive psychological functioning can be part of tailor-made programs promoting a healthy lifestyle (26), i.e., an exercise program for one patient while another might benefit from working on social skills or cognitive therapy approaches to optimize positive thoughts (26). Several studies are currently focusing on the effectiveness of positive psychology interventions (e.g., a resilience training program) in cardiac patients (55, 56).

The results of the current study should be viewed in light of its limitations and strengths. First, information about psychological functioning and adherence was assessed via self-report instruments, which may not reflect actual psychological functioning and adherence. Second, the present study included *two* constructs of positive psychological functioning (optimism and positive affect). So future work should include more and different types of positive constructs, e.g. "*resilience*": a measure for psychological hardiness, which is used to describe individuals' behavior in stressful situations, based on engagement towards life, control of life and readiness to overcome challenges in life (57). More examples include "*vitality*" (enthusiastic zest for life and the capacity for regulation), "*purpose in life*" (extent to which individuals have purpose and meaning in their lives) and "*Ikigai*" (a Japanese concept; having a life worth living) (58-60). Future work could also include (psycho)social concepts, such as social support, work (stress), family etc. Knowing more about the role of these concepts might help in *strengthening patient's resources* in clinical practice (43). Third, as mentioned earlier, the current study included information about patients' *affective states* and patients' *traits* (i.e. optimism), so in future research it might be an important addition to focus more on state-trait differences. Finally, further research could incorporate distinct theoretical approaches characterizing well-being, e.g., the difference between eudaimonic (fulfilling one's potential and meaningful life pursuits) and hedonic (pursuit of pleasure and happiness) well-being (39, 61). However, key strengths of the current study are its clearly defined and relatively large patient population, representing an important part

of the cardiovascular patients. Besides, for adherence a longitudinal design was used and finally all questionnaires were validated, reliable and have been used frequently in different cardiovascular patient groups.

In conclusion, for coronary artery disease patients it is important to assess both negative (e.g., depression, anxiety) and positive psychological factors (e.g., optimism). This will represent a more complete view of a patients' psychological functioning. Besides, assessment of positive psychological factors may open up new avenues for treatment. Interventions focusing on psychological well-being can increase a patient's capacity which can in turn induce better self-care (e.g., better treatment adherence). Additional research is needed to investigate the relationship between positive psychological factors and other cardiac outcomes, such as cardiac events and mortality.

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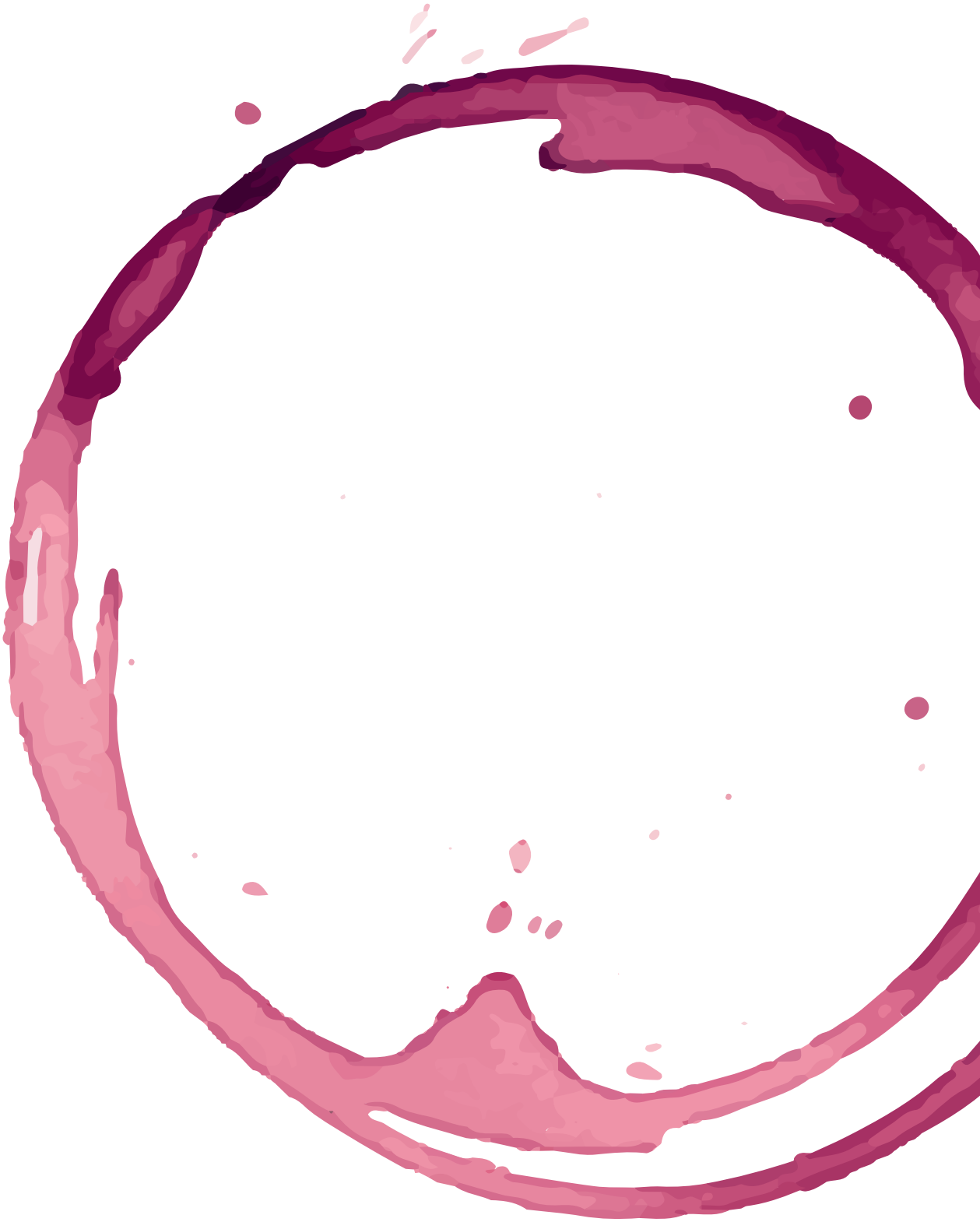

Chapter 6

Stress resilience, optimism and emotional adaptation in the immediate period after percutaneous coronary intervention – results from the THORESCI study

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ABSTRACT

Background: Large individual differences exist in the degree of emotional adaptation after an acute coronary event, which may partly be explained by individual differences in dispositional characteristics. Optimism and trait resilience are dispositional traits that may have a favorable effect on health outcomes. We examined the association of trait stress resilience, optimism and pessimism with emotional recovery after acute, sub-acute or elective percutaneous coronary intervention (PCI) during the first 6 months thereafter.

Methods: Patients undergoing PCI (N=831, mean age=64.2±10.1; 78% male) filled out psychological surveys during hospital admission and at 1 and 6 month follow-up to assess trait resilience (DRS-15), optimism and pessimism (LOT-R) as dispositional traits and depressive (PHQ-9) and anxiety (GAD-7) symptoms. Response profiles were calculated, rendering a resilient, emerging, recovering and persisting depression/anxiety response. Multinomial regression was used to assess the predictive value of optimism, pessimism and trait stress resilience, while adjusting for demographic and clinical covariates.

Results: Regarding the response profiles, 55/59% of stable CAD/stabilized ACS patients and 54/53% of unstable ACS patients had a resilient depression/anxiety response. Anxiety and depression profiles correlated .61 in stable CAD/stabilized ACS patients and .70 in unstable ACS patients. In multivariable analyses, higher optimism was protective for most post-event depression and anxiety response profiles, while pessimism was associated with persisting emotional distress and delayed emotional responding, independent of clinical and demographic covariates. Lack of trait stress resilience only had added value in predicting the persisting depression and anxiety profiles.

Conclusion: Relatively stable positive and negative personality traits are associated with depression and anxiety response profiles after a coronary event, which has to be taken in consideration when choosing type and timing of treatment.

INTRODUCTION

Coronary artery disease (CAD) is a major cause of death and health care burden worldwide (1) and is associated with reduced quality of life. Suffering from CAD is taxing, and requires both physical and mental recovery. Although considerable improvements in prophylaxis and treatment of CAD has reduced morbidity and mortality significantly over the past decades (2), patients experiencing emotional distress after a coronary event, such as significant anxiety or depression, do not seem to benefit as much as might have been expected (3, 4). In patients with CAD, the prevalence of depression is high, and increases with the acuteness of the cardiac condition, varying between 20% in stable CAD patients to 40% in patients recovering from acute coronary syndrome (5). Moreover, depression in cardiac patients is persistent, with prevalence rates being rather constant over time (6, 7). Though anxiety is less studied in CAD patients, its importance as a cardiac risk modifier must not be underestimated. Anxiety also is highly prevalent in CAD patients (8), and seems to be an independent risk factor for incident CAD and cardiac mortality (9). The course of anxiety is relatively stable for the majority of CAD patients (10).

Substantial individual differences exist in the level of emotional adaptation after an acute coronary event. After a traumatic event, such as myocardial infarction or cardiac revascularization, the emotional response may be shaped in differential profiles (11). Trauma theory shows that while some individuals seem unaffected by the event (i.e., resilient response), others will show an emotional response (either immediate or delayed) that will eventually recover. A further subgroup may show persisting levels of chronic distress (11). A recent study identified these four trajectories of depressive symptoms after myocardial infarction empirically, and reported a differential mortality risk associated with the trajectories. As compared to the resilient profile, post-MI patients with emerging or persistent depressive symptoms had lower chance of survival (12). Research has shown that the extent to which a person is able to successfully deal with acute events may in part be determined by dispositional traits (13, 14). More specific, positive traits like optimism and trait stress resilience may have a favorable effect on health outcomes (15, 16). Optimism is defined as a stable predisposition that determines the extent to which people hold generalized favorable expectancies for their future (13). Both, objective and subjective health in patients recovering from MI was reported to be better in patients who were more optimistic (15, 17-19). Optimism has also been related to a reduced incidence of cardiovascular disease (18, 19) as well as a survival benefit (15, 18), and a recent study has shown that the resilient post-MI trauma response was characterized by the presence of optimism (12). Pessimism to the contrary has been associated with increased depression in heart failure patients (20). Turning to trait stress resilience, which can be considered as the ability to successfully adapt to stress (i.e. “bounce back” from adversity or problems) (14), studies have shown stress resilience to be

associated with reduced risk of incident CAD (16). It is unknown whether trait stress resilience affects cardiovascular prognosis. Moreover, it is unknown how trait stress resilience relates to emotional response profiles. Knowing more about predispositional determinants of the emotional adjustment after percutaneous coronary intervention (PCI) for acute and less acute CAD is important for two reasons. For one, personality characteristics may affect the size of the emotional response as well as the speed of emotional recovery, which in turn may affect screening results used to allocate patients to adequate care trajectories. In addition, these determinants may be new interventional targets, as optimism and stress resilience go together with adaptive coping and emotion regulation strategies, which may be learned (21).

As there is a paucity of research on the effects of optimism/pessimism and trait stress resilience on emotional recovery in the immediate period after an acute coronary event, we examined the association of trait stress resilience, optimism and pessimism with emotional recovery after PCI during the first six months thereafter. We hypothesized that patients scoring high on trait optimism and trait stress resilience and low on pessimism would have a smaller emotional response to the cardiac event to begin with, and would show a more stable emotional functioning over time. In addition, we studied the potential moderating effect of the acuteness of the PCI, as only part of the procedures are performed for life-threatening cardiac events.

METHODS

Patient population and procedure – the THORESCI study

The current study was based on a large prospective observational cohort study, the '**T**ilburg **H**ealth **O**utcomes **R**egistry of **E**motional **S**tress after **C**oronary **I**ntervention (THORESCI)' study, which recruits participants from the clinical standard of care PCI Registry at the Elisabeth-TweeSteden Hospital at Tilburg, the Netherlands. First patients were included in December 2013, and the study is still actively recruiting. All patients scheduled for either elective or acute PCI for ≥1 coronary occlusions were included, provided that patients were aged ≥18 and had sufficient understanding of the Dutch language to fill out questionnaires. Patients with a life threatening comorbidity (e.g., metastasized cancer) or with a cognitive disorder were excluded from the study. On the day of the PCI, patients were approached by a member of the research team who explained the study content and its requirements. After giving written consent, the patients underwent a brief psychosocial screening interview, and were asked to fill out a set of validated psychosocial questionnaires just after PCI (between 0-5 days; baseline (T0)), and at 1 (T1), 6 (T2), 12 (T3), and 24 (T4) months post-PCI. The current study uses the first 3 measurement occasions. The study protocol is in keeping

with the Helsinki declaration (22) and approved by the institutional medical ethics review board (METC Brabant).

Measures

Demographic and clinical variables

Demographic (age and sex) and clinical variables related to the PCI procedure (indication, single vs. multivessel PCI), cardiac history (previous PCI, CABG surgery, and/or myocardial infarction (MI)) and prescribed medications were extracted from the patients' medical records at baseline. Patients admitted for elective PCI or for PCI after stabilized angina, or stabilized myocardial infarction were classified as having a PCI in a non-life-threatening situation, while PCI for unstable acute coronary syndrome (either unstable angina, or MI with ST elevation, or non-ST elevation MI) was considered a PCI in a life-threatening situation. Educational attainment was assessed with a dedicated self-report question asking for the highest completed level of education. For computational purposes we then split the responses into two categories, i.e. at least vocational education vs. high school or less.

Optimism & pessimism

Optimism and pessimism were assessed at baseline by using the revised version of the Life Orientation Test (LOT-R) (23), a widely used measure of optimistic traits evaluating generalized expectations of positive and negative outcomes. The LOT-R includes 4 fillers and 6 actual statements, of which 3 assess optimism (e.g., '*In uncertain times, I usually expect the best*') and 3 assess pessimism (e.g., '*If something can go wrong for me, it will*'). Responses to statements are given on a 5-point Likert scale (i.e. 1 'I disagree a lot') to 5 ('I agree a lot')), with a higher score referring to greater optimism or greater pessimism depending on the subscale. Because prior studies have shown that adhering to a bipolar model, in which you include both optimism and pessimism together in a single scores seems to mask each other effects (24). Therefore, in our analyses we used the independent optimism component subscale scores and the pessimism component subscale scores separately (Cronbach's alpha .69 for both). A median split was calculated (cut-offs optimism: 8.0; pessimism: 5.0) to examine prevalences of above median scores in the depression and anxiety response profiles.

Stress resilience

The Dispositional Resilience Scale (DRS-15) was used to determine stress resilience, as a generalized style of functioning including cognitive, emotional and behavioral qualities (25), at baseline. This 15-item measure comprises three components of hardiness: challenge (i.e. seeing change and new experiences as exciting opportunities to learn and develop),

commitment (i.e. tendency to see the world as interesting and meaningful) and control (i.e. belief in one's own ability to control or influence events). Positively and negatively worded items are rated on a 4-point Likert scale from 0 ("not at all true") to 3 ("completely true"). For the current study, Cronbach's alpha was good, at .78. A median split was calculated (cut-off: 29.0) the prevalence of trait stress resilience in the depression and anxiety response profiles.

Depression

Depressive mood was assessed using the reliable and valid Patient Health Questionnaire 9 (PHQ-9) at baseline, one, and 6 months post-PCI (26). This questionnaire consists of 9 items (e.g., "Little interest or pleasure in doing things"), based on the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria of depression. Items are rated on a 4-point Likert scale from 0 ("not at all") to 3 ("almost every day") (26). For major depressive disorder the recommended cut-off score is ≥10 (26). In the present study, the internal consistency of the PHQ-9 ranged between .86 and .88.

Anxiety

Symptoms of anxiety were appraised using the Generalized Anxiety Disorder 7-item (GAD-7) at baseline, one, and 6 months post-PCI. This is a valid and efficient tool to screen for generalized anxiety (27). The 7 items of this instrument are scored on a 4-point Likert scale form 0 ("not at all"), to 3 ("almost every day") (27). To determine anxiety, the recommended cut-off score is ≥10 (27). In the current study, Cronbach's alpha was excellent (.91 (T0 and T1) and .92(T2)).

Statistical analysis

Descriptive statistics were calculated for the complete group of participants, and included means (SD) for continuous variables and percentages for categorical variables. Pearson correlations were used to interrelate the personality scores, and Spearman correlations were used to assess the relation between depression and anxiety response profiles. Pearson Chi squares tested differences in above median prevalences of the personality traits in the different depression and anxiety response profiles.

Calculation of response profiles – To construct the 4 response profiles commonly seen after a (medical) trauma, we used a cut-off of 5, indicating mild depressive or anxiety complaints, at each measurement occasion to discriminate between present or absent depressive or anxiety complaints. If patients reported values <5 at all measurement occasions, they were included in the *resilient profile*. If patients reported values >5 at all measurement occasions, they were considered as *persistent*. In case of increasing symptoms from below to above the cut-off of 5 from measurement occasion 1 to 2 and 3 or from 1 to 3, patients

were classified as having an *emerging* response pattern. Finally, when patients recovered from measurement occasion 1 (above cut-off) to 2 (below cut-off) or 3 (below cut-off), they were classified as having a *recovering* profile.

Analysis – We performed two multinomial hierarchical regression analyses with the respectively depression and anxiety response profiles (resilient, emerging, recovering, and persisting) as dependent variables. We used the resilient profile as a reference category. First, we entered the continuous optimism, pessimism and trait resilience scores to gauge the unadjusted effects of personality on response profile individually. Second, we added demographic (sex, education) and clinical covariates (history of CAD, comorbidities). We performed these analyses twice, once for patients with a PCI for non-threatening stable CAD or unstable angina, and once for patients undergoing PCI for a life-threatening myocardial event, as we had good reason to suspect that these groups are different. SPSS 22 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY) was used for all analyses and a p value of <.05 was considered significant.

RESULTS

Sample characteristics

Due to the ongoing nature of the study, the total of 831 patients were included at the time of the data extraction (February 2017), 718 provided the necessary baseline and follow-up data, while 14% (n=113) of patients only had baseline data or data at only one follow-up occasion, and were therefore not able to be classified in a profile. THORESCI at that time had a 71% response rate and a 17% 1-year attrition rate. Table 1 holds the descriptive statistics of the sample used for the current analysis. The sample consistent for the large majority of men (78%), with an average age of 64. About half of the patients had a history of coronary heart disease. Regarding the response profiles, 55% (N=206) of stable CAD/stabilized ACS patients and 54% (N=182) of unstable ACS patients had a resilient depression response. A total of 59% (N=221) of stable CAD/stabilized ACS patients and 53% (N=183) unstable ACS patients had a resilient anxiety response. Anxiety and depression profiles correlated .61 in stable CAD/stabilized ACS patients and .70 in unstable ACS patients.

Figure 2 displays the depression and anxiety response profiles for the patients with a non-life-threatening (upper panel) and life-threatening (lower panel) reason for their PCI. Crosstabs showed a significant difference in the presence of optimism (above median) between resilient and other response profiles in a dose response relationship (depression: Chi square = 61.50; p<.0001; anxiety: Chi square = 72.76; p<.0001; Figure 1). For trait stress resilience a similar difference was found (depression: Chi square = 62.20; p<.0001; anxiety: Chi

Table 1. Baseline patient characteristics

N	831
Demographics	
Sex (% men)	78% (646)
Age Mean (SD)	64.2 (10.1)
Partner status (with partner)	81% (671)
Educational attainment (≤ high school)	32% (267)
Cardiovascular risk factors	
Smoking (yes)	12% (101)
CVD before age 60	38% (287)
Diabetes	21% (154)
Hypercholesterolemia	34% (251)
Hypertension	43% (318)
Obesity	29% (219)
Clinical variables	
Cardiac history (yes) [a]	48% (356)
Previous MI	30% (221)
Previous PCI	42% (314) (includes first PCI in a series in included at second or third PCI in the series)
Previous CABG	7% (53)
Chest pain complaints	37% (279)
PCI indication (elective/UA/STEMI/nonSTEMI)*	25% (204) / 19% (155) / 32% (259) / 23% (191)
Heart Failure	2% (14)
Multivessel PCI	18% (152)
Comorbidities (1 or more)	39% (327)
CR participation	33% (270)
Medication at admission	
ACE inhibitors/ARB	30% (164)
Beta blocker	29% (160)
Calcium antagonist	12% (66)
Diuretics	15% (80)
Psychotropic medication prescription	10% (80)

Numbers represent % (N) unless otherwise indicated. a cardiac history includes previous myocardial infarction and/or coronary intervention (PCI or CABG).

square = 44.67; p<.0001; Figure 1). For pessimism, relations were opposite, with pessimism being more prevalent in all depression response profiles in comparison to resilient profile, and in emerging and persisting anxiety profiles (depression: Chi square = 33.93; p=<.0001; anxiety: Chi square = 36.33; p<.0001; Figure 1).

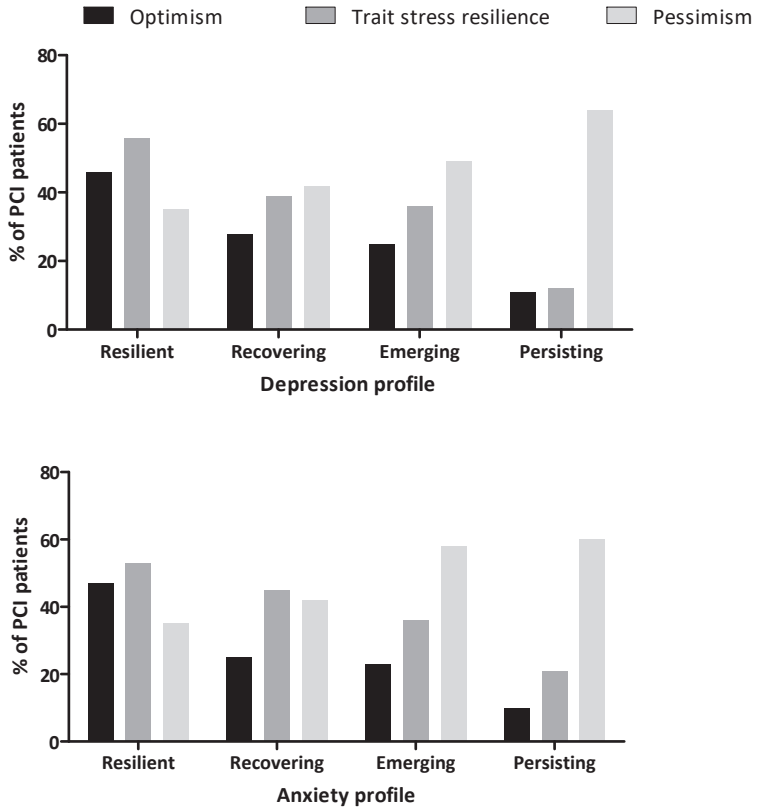

Figure 1. Prevalence (%) of above-median personality characteristics by response profile.

Personality correlations

Optimism, pessimism and stress resilience facets showed low correlations (Table 2), with both optimism (r=.44) and pessimism (r=-.30) correlating highest with the commitment facet of resilience. These low correlations indicate that these personality traits share little variance, and thus may be included in the same prediction models.

Depression

In univariate analysis (Top panel Table 3), higher levels of optimism and trait resilience in patients with stable CAD or stabilized ACS were protective for developing an emerging or persisting depression profile, and were associated with existing depressive complaints that waned off over the 6-month follow-up period (recovering profile). In patients with a life-threatening event (i.e. unstable ACS), optimism and trait resilience were solely protective

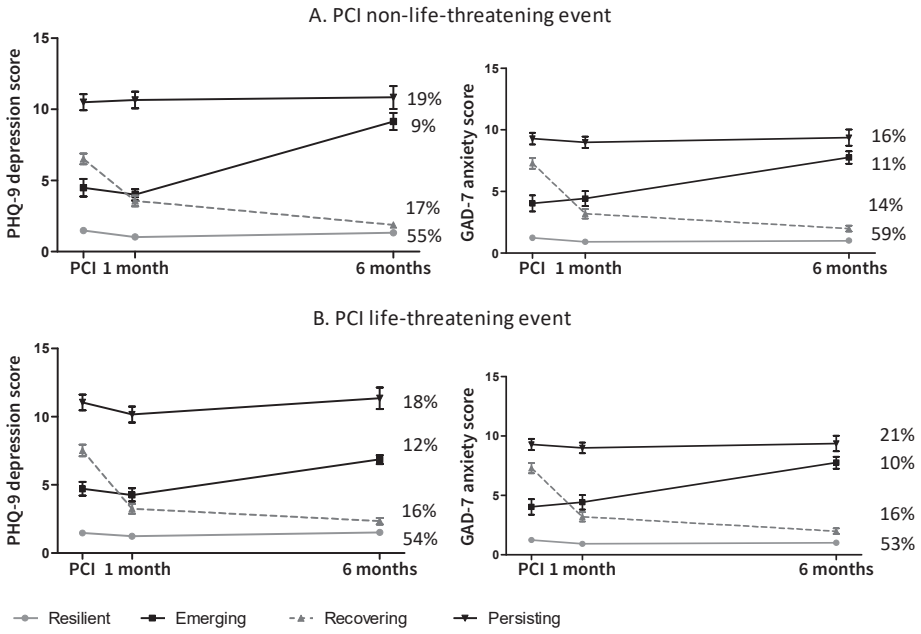

Figure 2. Depression and anxiety profiles for non-life threatening and life-threatening events.

Table 2. Personality scores and their intercorrelations

	LOT-R: Optimism/pessimism		DRS: Stress resilience			
	Optimism	Pessimism	Challenge	Commitment	Control	Total
Mean (SD)	7.5 (2.3)	5.0 (2.6)	7.9 (2.4)	11.2 (2.5)	10.1 (4.0)	29.2 (6.5)
Correlations						
Optimism	-	-.13***	.21***	.44***	.18**	.35***
Pessimism	-	-	-.24***	-.30***	-.11**	-.28***

for the persisting depression profile, while there were unrelated to the remaining profiles. Higher levels of pessimism were associated with a persisting depression profile in the stable/stabilized patients, while pessimism was predictive of having an emerging and persisting depression profile in with a life-threatening event.

When adjusting for clinical and demographic covariates (Lower panel Table 3), the relations of trait resilience, optimism and pessimism with the depression profiles were unaltered in size, although the association of trait resilience with the recovering profile became non-significant in adjusted analysis. Women were more likely to show a recovering

Table 3. Multinomial regression of depression response profiles

	PCI for non-life threatening coronary occlusion or stabilized ACS [a]						PCI after life threatening nonstable ACS [b]					
	Emerging (N=32)		Recovering (N=60)		Persisting (N=62)		Emerging (N=41)		Recovering (N=49)		Persisting (N=53)	
	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p
Univariate relations												
Optimism	**.79 (.66-.76)**	**.016**	**.83-(.72-.96)**	**.013**	**.73 (.62-.85)**	**<.0001**	.93 (.78-1.11)	.394	.92 (.78-1.08)	**.288**	**.60 (.50-.73)**	**<.0001**
Pessimism	1.08 (.91-1.27)	.377	*1.11 (.98-1.26)*	*.096*	1.22 (1.07-1.40)	.003	**1.23 (1.07-1.42)**	**.005**	1.10 (.96-1.26)	.157	**1.26 (1.08-1.48)**	**.004**
Trait resilience	**.91 (.84-397)**	**.005**	**.95 (.90-.997)**	**.04**	**.90 (.85-.95)**	**.0002**	.95 (.90-1.01)	.133	.95 (.89-1.01)	.056	**.90 (.84-.96)**	**.001**
Multivariable relations												
Optimism	**.77 (.63-.95)**	**.012**	**.83 (.71-.98)**	**.026**	**.72 (.60-.86)**	**<.0001**	.90 (.75-1.08)	.266	.92 (.78-1.09)	.330	**.61 (.50-.74)**	**<.0001**
Pessimism	1.02 (.85-1.22)	.840	1.08 (.94-1.23)	.281	**1.21 (1.04-1.42)**	**.015**	**1.25 (1.07-1.45)**	**.005**	1.14 (.98-1.31)	.091	**1.31 (1.10-1.53)**	**.002**
Trait resilience	**.90 (.84-.97)**	**.008**	.95 (.90-1.01)	.092	**.88 (.83-.94)**	**<.0001**	.96 (.91-1.03)	.258	.95 (.89-1.01)	.075	**.91 (.85-.97)**	**.005**
Male sex	.79 (.27-2.35)	.675	**.39 (.18-.87)**	**.021**	**.37 (.16-.86)**	**.021**	.50 (.21-1.17)	.108	.61 (.27-1.38)	.231	**.29 (.13-.66)**	**.003**
Lower education	.84 (.33-.2.18)	.723	1.34 (.65-2.76)	.431	.60 (.26-1.36)	.219	1.12 (.51-2.47)	.766	.68 (.31-1.50)	.336	.79 (.35-.1.80)	.573
Cardiac history	.98 (.42-2.30)	.984	.58 (.29-1.15)	.120	.79 (.38-1.63)	.515	1.37 (.65-2.89)	.432	.94 (.48-1.87)	.868	1.27 (.58-2.76)	.549
Comorbidity	1.77 (.75-4.13)	.193	.97 (.49-1.89)	.975	1.12 (.54-.2.34)	.753	1.06 (.50-2.22)	.887	.90 (.44-1.81)	.761	1.07 (.49-2.34)	.873

[a] Reference group resilient profile N=158; [b] reference group resilient profile N=163.

Table 4. Multinomial regression of anxiety response profiles

	PCI for non-life threatening coronary occlusion [a]						PCI after life threatening nonstable ACS [b]					
	Emerging (N=33)		Recovering (N=54)		Persisting (N=59)		Emerging (N=33)		Recovering (N=54)		Persisting (N=72)	
	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p
Univariate relations												
Optimism	**.77 (.65-.92)**	**.004**	.86 (.74-1.00)	.057	**.65 (.55-.77)**	**<.0001**	**.77 (.64-.94)**	**.010**	**.74 (.63-.87)**	**<.0001**	**.64 (.54-.76)**	**<.0001**
Pessimism	**1.18 (1.02-1.37)**	**.026**	1.03 (.90-1.17)	.704	**1.25 (1.09-1.45)**	**.002**	1.12 (.94-1.31)	.191	1.10 (.96-1.25)	.189	**1.22 (1.06-1.40)**	**.006**
Trait resilience	.96 (.90-1.02)	.150	.98 (.93-1.03)	.410	**.94 (.89-.99)**	**.029**	.98 (.91-1.05)	.490	.98 (.92-1.03)	.412	**.91 (.86-.97)**	**.002**
Multivariable relations												
Optimism	**.76 (.62-.92)**	**.006**	.84 (.71-1.00)	.053	**.64 (.53-.78)**	**<.0001**	**.77 (.63-.94)**	**.010**	**.72 (.61-.85)**	**<.0001**	**.64 (.54-.76)**	**<.0001**
Pessimism	1.15 (.98-1.35)	.093	1.02 (.88-1.19)	.755	**1.21 (1.03-1.43)**	**.020**	1.12 (.94-1.34)	.195	1.11 (.96-1.27)	.568	**1.23 (1.06-1.43)**	**.006**
Trait resilience	.96 (.90-1.03)	.272	.97 (.91-1.02)	.236	**.92 (.87-.98)**	**.013**	.98 (.93-1.07)	.940	.99 (.93-1.05)	.723	**.91 (.86-.97)**	**.003**
Male sex	.59 (.24-1.49)	.268	.57 (.26-1.28)	.171	.74 (.30-1.83)	.516	.63 (.21-1.91)	.416	**.33 (.15-.72)**	**.006**	**.31 (.14-.69)**	**.004**
Education	1.08 (.46-2.51)	.864	.68 (.31-1.52)	.350	.50 (.21-1.18)	.112	.51 (.18-1.41)	.194	.75 (.35-1.62)	.460	.95 (.45-2.00)	.886
Cardiac history	.62 (.28-1.40)	.231	1.23 (.62-2.44)	.557	.96 (.45-2.04)	.922	.57 (.24-1.35)	.201	.76 (.38-1.52)	.441	.79 (.39-1.58)	.499
Comorbidities	.81 (.36-1.81)	.608	1.23 (.62-2.46)	.557	1.35 (.63-2.89)	.442	1.75 (.74-4.13)	.199	1.23 (.61-2.48)	.568	.65 (.31-1.36)	.253

[a] Reference group resilient profile N=171; [b] reference group resilient profile N=160.

or persisting depression profile in stable/stabilized PCI patients, and to show a persisting depression in PCI patients with unstable ACS. None of the other covariates were related to the depression profiles.

For stress resilience, a post-hoc analysis including resilience subscales showed that reduced commitment (tendency to see the world as interesting and meaningful) was the driving force behind the found associations (Stable CAD/Stabilized ACS: OR=.66 (.54-.81) p<.0001; Unstable ACS: OR=.57 (.46-.70) p<.0001; other subscales (Control & Challenge): NS).

Anxiety

For anxiety, results are presented in Table 4. In both patient groups, a relative lack of optimism was associated with all anxiety response profiles as compared to the resilient (non-responding) group, except for the recovering trajectory in the stable/stabilized patients, which showed a trend association. Across the board, pessimism and lack of stress resilience were associated with persistent anxiety.

This result remained unaltered when adding our a priori determined covariates to the model. Men were significantly less likely to show a recovering and persisting anxiety profile, but only after treatment for life-threatening nonstable ACS. For stress resilience, a post-hoc analysis including resilience subscales showed that reduced commitment (tendency to see the world as interesting and meaningful) was the driving force behind this association (Stable CAD/Stabilized ACS: OR=.73 (.60-.89) p=.002; Unstable ACS: OR=.62 (.52-.75) p<.0001; other subscales (Control & Challenge): NS).

DISCUSSION

The current study aimed to investigate the role of optimism, pessimism, and stress resilience as determinants of the emotional response trajectory after PCI. To this end, we examined response profiles in depression and anxiety over the first 6-months post-PCI. We found that optimism and trait resilience were highly associated with a resilient depression and anxiety response (low scores on all measurement occasions). Higher optimism was protective for most adverse post-event depression and anxiety response profiles, while pessimism was associated with persisting emotional distress and delayed emotional responding. In these multivariable analyses, lack of trait stress resilience predominantly had added value in predicting the persisting profiles (high scores on all measurement occasions).

Resilience is a complex phenomenon, as it can be defined as both predictor (i.e. personality or style) and outcome (i.e. lack of emotional response). In the face of loss or trauma, resilience, or the absence of an emotional response, is common (11, 28). Patients

may not show an emotional response, or even show post-traumatic growth. Optimism has shown to be a strong predictor of post-traumatic growth (28) and in our results, optimism was associated with a non-responsive profile with respect to anxiety and depression symptoms. Nonetheless, resilience is only one of multiple, qualitatively different, possible response trajectories, including recovery, late response (i.e. emerging), and persisting profiles (21). The results of the current study show that these emotional responses as described in loss and trauma literature may be extended to emotional reactions to medical events such as myocardial infarction or even revascularization procedures such as PCI. The current results show that a substantial part of patients had a small or even absent emotional response and stable psychological functioning in the 6 months post-PCI, and that these patients were characterized by high trait stress resilience and optimism. Patient-reported outcomes for these patients seem to be positive, as recent study showed a relation between higher optimism and lower depressive symptoms and better physical health status at 1 year post-ACS, independent of depression and demographic and clinical covariates. The prominent role of pessimism in the persistent emotional distress groups concurs with results from previous studies showing that pessimism is associated with health-damaging behaviors (29), and that depression in PCI patients from diverse indications was associated with a more pessimistic disease perspective (30).

A substantial percentage of patients with significant depression and/or anxiety levels during follow-up were characterized by pre-existing depression and/or anxiety, suggesting that the emotional distress was not event-induced. Nevertheless, these patients scored on average highest on the PHQ-9 and GAD-7 throughout the follow-up period. Prior studies have reported inconsistent findings with regard to the cardiovascular prognostic risks associated with persisting depression/anxiety. While there is some evidence that an event-related increase in depressive symptoms in particular has important predictive value for a poor prognosis, over persistency of symptoms (31, 32), other studies suggest quite the opposite, showing an increased risk for patients with persistent depressive or anxiety complaints (33). However, this latter study did not compare the persistent depression with emerging depression as was tested in the prior studies. Another recent study in post-MI patients using the same symptom profiles as the present study, showed that patients with emerging or persistent depressive symptoms had lower chance of survival (12). Whether similar risk profiles are associated with the currently reported emotional response profiles and their predictors is subject to further study with much longer follow-up, as at the moment, one year follow-up mortality rate in the current sample is 2% (n=17).

With respect to our hypothesized moderator, stable CAD/stabilized ACS patients were similar to patients with an acute indication for PCI with respect to the prevalence of emotional response profiles, and somewhat different with respect to the effects of the predictors. Positive dispositional traits were more often predictive of the depression and

anxiety response profiles in the stable CAD/stabilized ACS patients as compared to the patients with an acute indication, while pessimism showed somewhat stronger relations with depression in the acute subgroup. Differences, though, were not as large as we first had hypothesized. An explanation for our observation might be that the response profiles may have different underlying mechanisms in the two groups. While in the acute patients, fear of dying might instigate the depression and anxiety response (34), in patients who received a PCI for stable CAD or in stabilized condition (being admitted to hospital on medication for several days) reasons underlying mechanisms might be more cognitive.

Our results further showed that women were more likely to be in recovering and persisting depression/anxiety profiles, indicating that female patients were more likely to have preexisting substantial depressive or anxiety symptoms, or have an immediate emotional response that subsided over the first month post-MI. This is in concurrence with studies on emotional adaptation after trauma that have suggested that there are sex differences in both preexisting psychopathology and the post-event emotional response, with women being more vulnerable of developing stress related disorders (35). Recent empirical studies examining potential mechanisms underlying these sex differences suggest a u-shaped neuromodulatory role of estrogen in fear processing (36), which is worth further investigation in the (mostly) post-menopausal female cardiac patients.

Current findings have clinical implications, as they point towards the recommendation to carefully screen individuals at multiple post-event time points so that the patients in the delayed response and persisting profiles get the psychological treatment they need. In addition, part of the patients will show natural post-event recovery, and will unnecessarily be treated when screening is performed too early. Results further point out that personality is an important determinant of the emotional response to MI/PCI. Both optimism and trait resilience have demonstrated the ability to function as a buffer to the exposure to a potentially traumatic medical event, with is consistent with a growing body of evidence (11). Clinical treatment could learn from adaptive mechanisms and emotion regulation strategies in these optimistic and resilient patients to inform new or improved treatment strategies. For example, when a positive outlook on life does not come innately, a person could still achieve this through making an effort to cognitively reappraise negative events by focusing on the positive aspects, which is an often used technique in psychotherapy. On the contrary, specific cognitions or behaviors that are associated with pessimism could be treated with elements from cognitive behavioral therapy, such as increasing pleasurable activities (37), or by applying techniques from mindfulness based cognitive therapy, such as practicing unconditional self-acceptance, applying compassion, generosity and love to oneself (38).

Future research may want to focus on several gaps in the current knowledge. There is still too little knowledge on what factors determine post-medical event emotional response profiles. Moreover, research that has been done regarding the prognostic significance of the

emotional response profiles have produced inconsistent findings. In addition, more studies into the mechanisms of resilience in the face of medical trauma/events, e.g., positive affect, coping and self-efficacy mechanisms (21), are warranted.

Current findings should be viewed in light of their limitations and strengths. The current sample was not complete, as the study is still ongoing. Further, post-PCI recovery requires physical and emotional adaptation. After 1 month post-PCI, all patients were offered a 6 to 12-week cardiac rehabilitation, during which a screening-selected part of the patient group received psychological group-counseling in addition to the physical therapy and life-style advice. At 6 months, patients are expected to have completed cardiac rehabilitation. We chose this shorter term follow-up period to be able to determine whether optimism and stress resilience could predict individual differences in mood profile during this period. Participation to cardiac rehabilitation (at least the psychological functioning module) might have affected the results, although a minority of patients participated in the psychological functioning module. Strengths of the study include the large, consecutive, real-world sample of PCI patients, and the broad and standardized assessment procedures.

In conclusion, the current study showed that a large part of patients show a resilient (i.e. absent) emotional response to PCI for life-threatening (i.e. unstable ACS), and non-life-threatening reasons (i.e. stable CAD and stabilized ACS), which was associated with increased optimism and trait stress resilience. Optimism and strait stress resilience were associated with a decreased likelihood of having a depression and/or anxiety response profile. Future research should consider examining the prognostic significance of individual differences in emotional response profiles and search for mechanisms associated with resilient responding.

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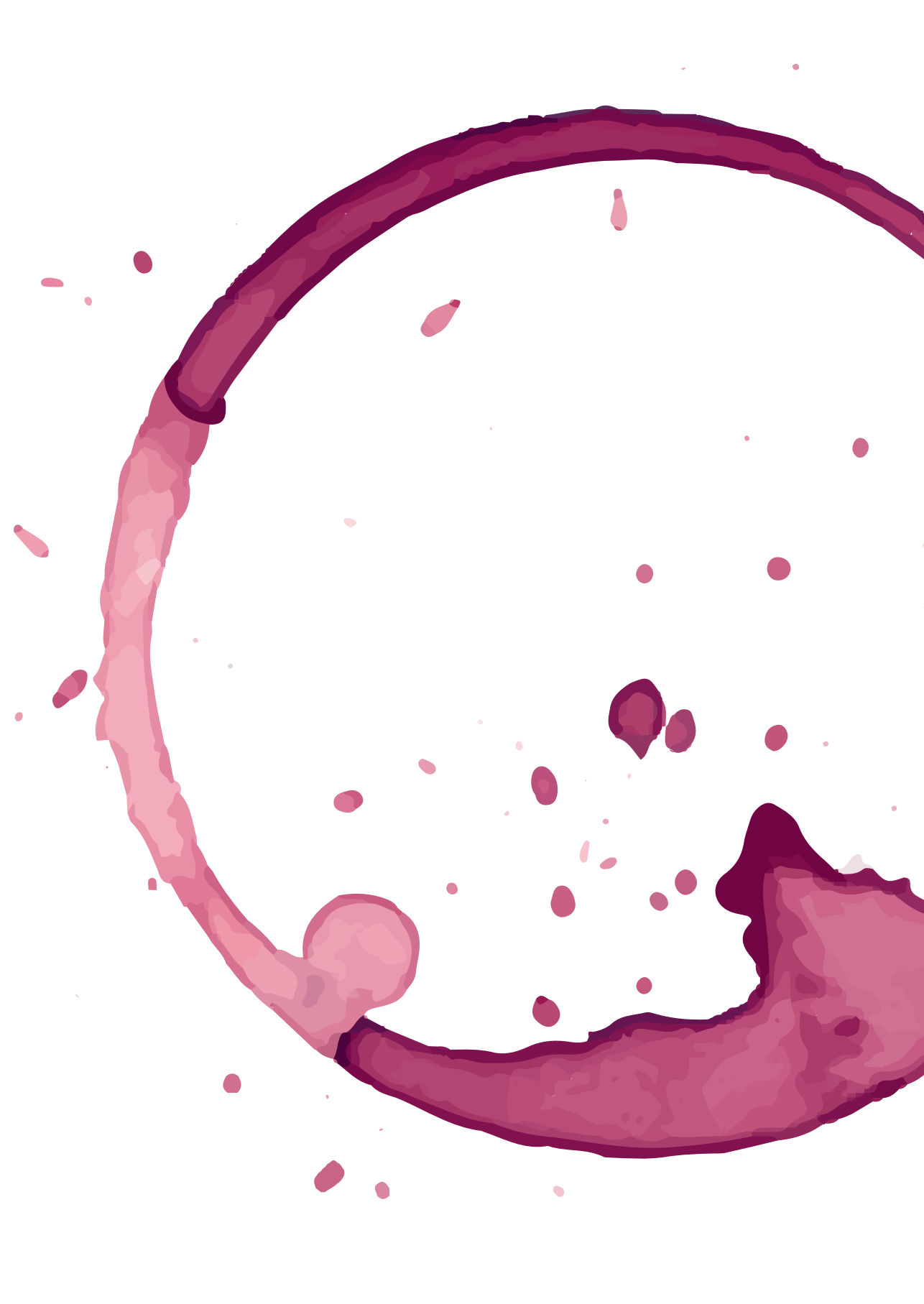

Chapter 7

Insight in non-participation and drop-out among coronary artery disease patients in a prospective cohort study – the THORESCI study

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Manuscript

ABSTRACT

Aim: We focused on the demographic, disease-related and psychological patient characteristics of those who refused to participate in the study ("refusers"), and those who quit the study during follow-up ("drop-outs"), and compared these with study participants. We also examined whether these three groups were differently associated with starting cardiac rehabilitation and mortality.

Method: Participants who dropped out (n=376; mean age=67.5±122; 70% men), and refusers (n=148; mean age=71.8±12.6; 69% men) were compared with active participants (n=865; mean age=65.1±11.8; 79% men). Demographics, clinical risk factors, medical history, participation to cardiac rehabilitation (CR), and mortality were obtained from patients' medical records and baseline questionnaires. Information about psychological symptoms (GAD-7, PHQ-9, DS14) was derived from medical records for patients who started CR in hospital. For patients who did not participate to CR but who participated in the study, psychological data were completed with study questionnaire data.

Results: Compared to participants, refusers were older (OR=1.04; 95% CI: 1.02-1.07; p=.002), had a lower socio-economic status (OR=2.78; 95% CI: 1.52-5.07; p=.001) were more often smokers (OR=1.64; 95% CI: 1.04-2.58; p=.03), and experienced a larger burden of illness (cardiac history: OR=1.56; 95% CI: 1.03-2.37; p=.04; non-cardiac history: OR=1.97; 95% CI: 1.24-3.13; p=.004). Refusers also participated less often in CR, independent of age and sex (OR=.69; 95% CI: .48-.99, p=.04). They also showed increased mortality as compared to patients who initially decided to participate (10% vs. 5%; OR=2.09; 95% CI: 1.14-3.85, p=.02). Compared to participants, drop-outs were more often women (OR=1.48; 95% CI: 1.08-2.03, p=.02). In drop-outs, increased levels of smoking (OR=1.51; 95% CI: 1.13-2.02, p=.01), and a larger burden of illness were found (non-cardiac history: OR=1.31; 95% CI: 1.00-1.71; p=.05). We did not find any differences between the groups regarding psychological symptoms.

Conclusion: Refusers and drop-outs differed systematically on some demographics and disease-related factors, which was translated into poorer health outcomes, as there were differences in the mortality risk of refusers versus participants. Therefore, we conclude that results from survey studies examining the association between psychosocial factors and health outcomes may underestimate the effects, as a healthier sample is participating than is present in the real life population.

INTRODUCTION

The association between psychological factors and (patient reported) outcomes in coronary artery disease (CAD) usually is examined using a prospective cohort design (1-6). Most of these studies report only on study participants instead of the whole potential participation population. Study participants may systematically differ from patients who refuse to participate (called "refusers" in the remainder of this paper) or from patients who are lost to follow-up due to attrition ("drop-outs") (7). This threat to internal validity and generalizability of the study findings is called "selection bias" (8). Selection bias may arise when specific patient characteristics (e.g. demographis, disease severity, psychological factors, comorbid diseases) interfere with patients' motivation for study participation or completion (7). For example, the clinical trials literature has reported that older adults, African Americans, and persons with less than a high school education may be reluctant to participate in research (9-11).

Studies in both the general population (12) and in CAD patients (13, 14) have shown an elevated mortality rate during follow-up among drop-outs as compared to participants who completed all study phases (12-14). Another study in post-MI patients has demonstrated that individuals who selectively responded to parts of psychosocial questionnaires were at increased risk for mortality as compared to participants who completed psychosocial questionnaires (14). A study in the Danish general population demonstrated higher morbidity and mortality among individuals who refused to participate in a health survey than in participants (15). Another general population based study also found mortality to be higher in participants than in refusers (16). However, in this study, CAD was more prevalent among participants than in refusers (16). It was suggested that worries about the disease may have increased the likelihood to participate (16).

Previous studies mostly reported on systematic differences regarding demographic and medical characteristics, but few studies have focused on systematic differences in the prevalence of psychological symptoms, while these may affect patients' considerations to participate, to refuse or to quit the study early. One study demonstrated an association between nonparticipation and higher levels of Type D personality (combination of negative affectivity and social inhibition) (17). In another study, it was shown that refusers had higher levels of neuroticism, and scored lower on conscientiousness, extraversion, and agreeableness than study participants (18). Also more transient psychological symptoms, such as depressive or anxiety symptoms, may act as barriers for study participation or completion. This is particularly a problem when psychological variables are the factors under study. In the Tilburg Health Outcomes Registry of Emotional Stress in Coronary Intervention (THORESCI), a large prospective cohort design to examine the relation between psychological factors and prognosis after percutaneous coronary intervention, we are in the

unique opportunity to compare all three groups (participants, refusers and drop-outs), with respect to demographic and medical characteristics, but also to psychological differences in a subsample of refusers, who filled out a psychosocial screener for the cardiac rehabilitation intake in hospital.

In the current study, we focused on the demographic, disease-related and psychological patient characteristics of those who refused to participate ("refusers"), and those who quit participation during follow-up ("drop-outs"), and compared these with study participants. We also examined whether these three groups were differently associated with starting cardiac rehabilitation and mortality.

METHODS

Patient population and procedure – the THORESCI study

The **T**ilburg **H**ealth **O**utcomes **R**egistry of **E**motional **S**tress after **C**oronary **I**ntervention (THORESCI) recruits participants from the clinical standard of care Percutaneous Coronary Intervention (PCI) Registry at the St. Elisabeth-TweeSteden Hospital in Tilburg, the Netherlands. All patients who were scheduled for either elective or acute PCI for one or more coronary occlusions between December 2013 and September 2017 were approached for study participation. Eligible patients were adults with sufficient understanding of the Dutch language to fill out questionnaires. Patients with life-threatening comorbidities (e.g., metastasized cancer) or severe cognitive disorders (e.g., dementia) were excluded. On the day of the PCI, patients were approached by a member of the research team who explained the study content and its requirements. After providing written consent, the patients were asked to fill out a set of validated psychosocial self-report questionnaires, spread over multiple measurement moments post-PCI. For the current study, active participants who were still in the study waiting for their next questionnaire at the time of data extraction were defined as "*participants*". "*Drop-outs*" were patients who participated at baseline in the THORESCI study, but quit the study during follow-up. Patients who refused to participate in the study were asked for permission to extract data from their hospital medical records, and these who gave consent and were defined as "*refusers*". The study protocol is in line with the Helsinki declaration and was approved by the institutional medical ethics review board (METC Brabant).

Characteristics of refusers and drop-outs versus participants

Demographics – Age and sex were obtained from patients' medical records at baseline. For refusers, marital status was extracted from patients' cardiac rehabilitation file (when

available), for the others, marital status was reported as part of the baseline questionnaire. Socio-economic status (SES) was derived from patients' "status score". Information about status score was extracted from data collected by the Netherlands Institute for Social Research (SCP), downloaded in November 2017 from http://www.scp.nl/Formulieren/Statusscores_opvragen. The status score is based on postal code (extracted from patients' medical records), and calculated from four variables, including the mean income, percentage of habitants with a low income, percentage of habitants with low education, and percentage of habitants being unemployed in that district. All districts are ranked according to their social status in low, middle, and high. Middle SES was used as reference category.

Clinical risk factors – Clinical risk factors included diabetes mellitus type 2, hypercholesterolemia, hypertension, and smoking status. For participants and drop-outs, this information was extracted from patients' questionnaires and when data were missing, this information was completed with information from patients' cardiac rehabilitation file. For refusers, clinical risk factors were extracted from patients' cardiac rehabilitation file.

Medical history – Information about cardiac and non-cardiac medical history was obtained from patients' medical records. Cardiac history was defined as previous myocardial infarction, percutaneous coronary intervention, and/or coronary artery bypass grafting. Non-cardiac medical history was determined as cerebrovascular accident, transient ischemic attack, peripheral arterial disease, chronic obstructive pulmonary disease, kidney disease, rheumatism, and/or cancer.

Psychological symptoms – For all patients who started cardiac rehabilitation in hospital after February 2015, information about psychological symptoms was available from their medical records. At the start of cardiac rehabilitation, psychological symptoms are assessed in a telephone screening interview by a rehabilitation nurse. For patients who did not start cardiac rehabilitation in hospital but who participated in the THORESCI study, these data were completed with their self-report questionnaire data at one month. In cardiac rehabilitation and THORESCI, the same questionnaires for anxiety, depression, and Type D personality were used. Anxiety symptoms were estimated using the Generalized Anxiety Disorder (GAD-7) scale, a valid and efficient tool to screen for generalized anxiety (31). The 7 items (e.g., "Worrying too much about different things") are scored on a Likert scale form 0 (not at all), to 3 (almost every day) (31). We used the recommended cut-off score ≥10. In the current study, internal consistency was high (Cronbach alpha .89). To assess depression, the widely used Patient Health Questionnaire (PHQ-9) was used (29). This measure consists of 9 items (e.g., "Little interest or pleasure in doing things"), based on the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria of depression. Items are rated on a Likert scale from 0 (not at all) to 3 (almost every day) (29). We used the recommended cut-off score ≥10. In the present study, the internal consistency of the PHQ-9 was high (Cronbach alpha at .84). Type D personality was assessed with the 14-item Type D scale (DS14) (19).

Seven negative affectivity (e.g., "I am often in a bad mood") and 7 social inhibition (e.g., "I often feel inhibited in social interactions) items were rated on a 5-point Likert scale from 0 (false) to 4 (true). In the current study, internal consistency for Type D personality was high (Cronbach alpha at .89).

Outcomes – Information about starting cardiac rehabilitation in hospital and mortality data were obtained from patients' medical records.

Statistical analyses

Univariate and multivariable multinomial regression analyses were used to identify the characteristics of refusers and drop-outs versus participants. Research participation status (participant, refuser, drop-out) was defined as the dependent variable, and demographics (sex, age, SES, marital status), clinical risk factors (diabetes, hypercholesterolemia, hypertension, smoking), medical history (cardiac, non-cardiac), and presence of psychological symptoms (anxiety, depression, Type D personality) as independent variables, in three separate models. "Participants" were defined as reference group and were subsequently compared with "refusers" and "drop-outs". Age and the psychological symptoms were continuous variables. The other demographics, clinical risk factors, and medical history variables were dichotomous. To examine the association between refusal and drop-out with starting cardiac rehabilitation in hospital, univariate and multivariable logistic regression models were used. Due to the limited number of deaths in the sample, we only performed univariate logistic regression for the mortality data. All analyses were performed using SPSS 22 (IBM SPSS Statistics for Windows, Version 22. Armonk, NY: IBM Corp USA) and we adhered to a significance level of $p \leq .05$.

RESULTS

Sample characteristics

A total of 1754 patients were approached for participation. Of the 1241 patients (71%) who participated, 376 (30%) were lost to follow-up ("drop-outs") and 865 patients (70%) were actively participating ("participants"). 148 (9%) patients who refused participation gave consent to use their medical data ("refusers"). These three groups were compared on demographics, clinical risk factors, medical history, and psychological symptoms. A flow-chart is presented in Figure 1 and baseline characteristics are listed in Table 1.

Table 1. Baseline characteristics

	Participants (n=865) (Reference)		Refusers (n=148)		Drop-outs (n=376)	
Demographics	n	%	n	%	n	%
Age (years ± SD)	65.09	11.84	71.79	12.62	67.53	12.22
Men	687	79	103	69	263	70
Having a partner*	632	73	38	69	213	73
SES**						
Low	167	19	52	35	93	25
Middle	549	64	79	54	232	62
High	145	17	16	11	50	13
Clinical risk factors	n	%	n	%	n	%
Diabetes	163	22	32	26	73	22
Hypercholesterolemia	280	36	53	42	130	37
Hypertension	356	46	56	44	153	43
Smoking	205	26	37	36	117	35
Medical history	n	%	n	%	n	%
Cardiac[1]	377	48	86	66	174	49
Non-cardiac[2]	466	60	77	74	216	66
Psychological symptoms	Mean	SD	Mean	SD	Mean	SD
Anxiety***	4.01	4.52	4.66	5.06	4.48	4.70
Depression****	4.87	5.02	5.74	4.62	5.36	5.14
Negative Affectivity*****	7.37	6.03	8.58	6.34	7.95	5.98
Social Inhibition*****	8.53	6.32	9.29	6.47	8.68	6.57
Prognostic factors	n	%	n	%	n	%
Mortality	48	6	14	10	11	3
Cardiac rehabilitation in hospital	470	54	64	43	191	51

PCI = percutaneous coronary intervention; [1]previous myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting; [2]cerebrovascular accident, transient ischemic attack, peripheral arterial disease, chronic obstructive pulmonary disease, kidney disease, rheumatism, cancer. *participants: n=798, drop-outs: n= 290, non-participants: n=55, **participants: n=865, drop-outs: n=375, non-participants: n=148; ***participants: n=790; drop-outs: n=265, non-participants: n=39; ****participants: n=789, drop-outs: n=262, non-participants: n=38; *****participants: n=773, drop-outs: n=248, non-participants: n=38.

Characteristics of refusers

Half of the refusers did not give any reason to decline study participation (51%). The main reasons given for refusers by the other patients were too much work to complete the questionnaires (20%), not being interested (16%), being too ill or disabled (8%), or being too emotionally distressed (5%) (Figure 1). Demographics, clinical risk factors, medical history,

psychological symptoms, and information regarding prognostic factors are displayed in Table 1.

Demographics – Univariate analysis showed that older patients were more likely to refuse participation than younger patients (OR=1.06; 95% CI: 1.04-1.07, p<.01), as were women (OR=1.74; 95% CI: 1.18-2.56, p=.01), and patients with a low SES (OR=2.14; 95% CI: 1.00-4.61, p=.05). For patients who were single, a trend was observed towards increased risk of being a refuser (OR=1.70; 95% CI: .94-3.09, p=.08). In multivariable analysis, only age and low SES remained significantly associated with refusal (Table 2).

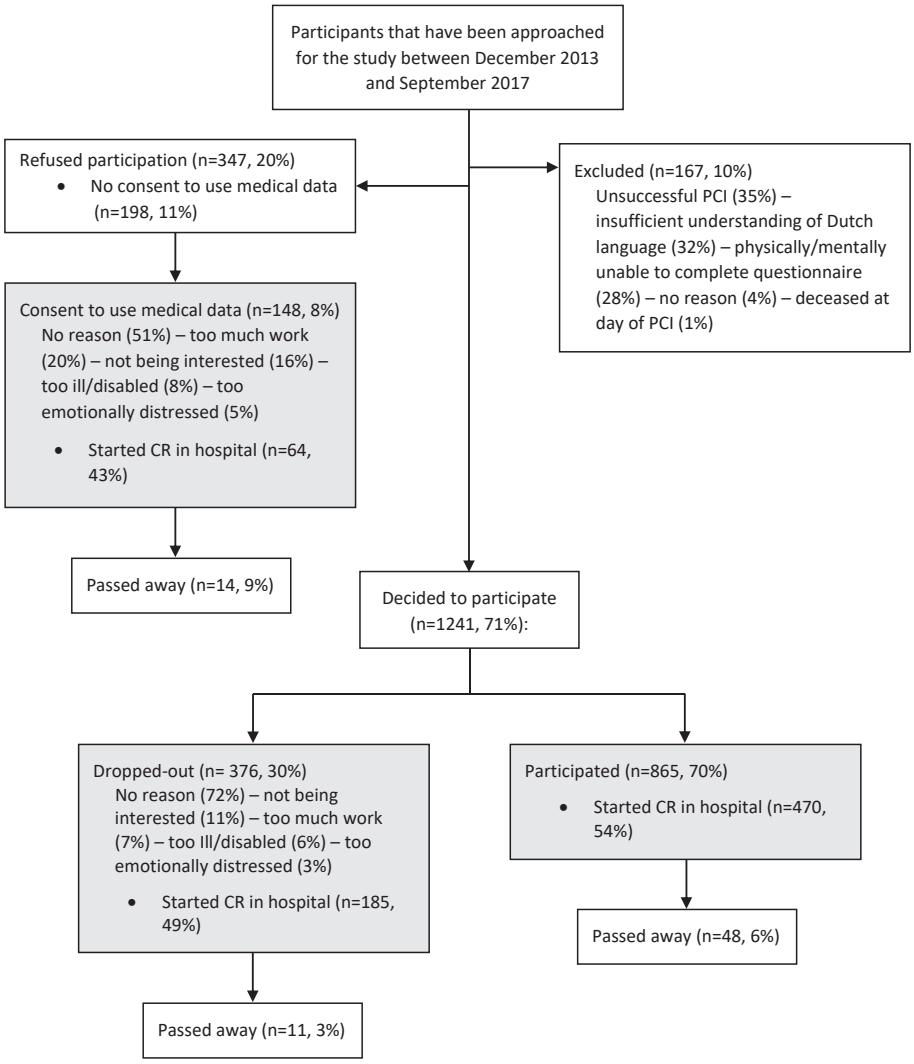

Figure 1. Flow-chart.
CR = cardiac rehabilitation.

Table 2. Demographics, clinical risk factors, and medical history as predictors of non-participation and drop-out as compared to participants in three separate models

	Refusers (n=148)			Drop-outs (n=376)		
Model 1. Demographics	B (SE)	OR (95% CI)	p	B (SE)	OR (95% CI)	p
Age	.04	1.04 (1.02-1.07)	**.002**	.01	1.01 (1.00-1.02)	.22
Female	-.22	.81 (.39-1.63)	.55	.39	1.48 (1.08-2.03)	**.02**
Not having a partner*	.29	1.37 (.71-3.16)	.37	.18	1.19 (.86-1.67)	.29
SES**						
Low	1.02	2.78 (1.52-5.07)	**.001**	.29	1.34 (.96-1.86)	*.09*
High	-.07	.93 (.37-2.32)	.88	-.14	.87 (.58-1.29)	.48
Note: R^2=.03 (Cox & Snel), .04 (Nagelkerke). Model $\chi^2(10)$=30.08, p=.001.						
Model 2. Clinical risk factors	B (SE)	OR (95% CI)	p	B (SE)	OR (95% CI)	p
Diabetes	.37	1.45 (.87-2.41)	.15	.06	1.06 (.76-1.50)	.73
Hypercholesterolemia	.36	1.43 (.91-2.25)	.12	.04	1.04 (.79-1.40)	.78
Hypertension	-.17	.85 (.53-1.35)	.48	-.12	.89 (.66-1.19)	.42
Smoking	.49	1.64 (1.04-2.58)	**.03**	.42	1.51 (1.13-2.02)	**.01**
Note: R^2=.02 (Cox & Snel), .02 (Nagelkerke). Model $\chi^2(8)$=15.63, p=.05.						
Model 3. Medical history	B (SE)	OR (95% CI)	p	B (SE)	OR (95% CI)	p
Cardiac[1]	.45	1.56 (1.03-2.37)	**.04**	-.09	.91 (.71-1.19)	.50
Non-cardiac[2]	.68	1.97 (1.24-3.13)	**.004**	.27	1.31 (1.00-1.71)	**.05**
Note: R^2=.02 (Cox & Snel), .02 (Nagelkerke). Model $\chi^2(4)$=16.40, p=.003.						

PCI = percutaneous coronary intervention; [1]previous myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting; [2]cerebrovascular accident, transient ischemic attack, peripheral arterial disease, chronic obstructive pulmonary disease, kidney disease, rheumatism, cancer. *participants: n=798, drop-outs: n=290, non-participants: n=55, **participants: n=720, drop-outs: n=253, non-participants: n=37.

Clinical risk factors – Univariate analysis showed that smokers were more likely to refuse participation (OR=1.61; 95% CI: 1.05-2.49, p=.03). Diabetes, hypertension, and hypercholesterolemia were not associated with refusal (all p-values >.20). In a multivariable analysis, smoking was still significantly associated with refusal (Table 2).

Medical history – Univariate analysis demonstrated that patients with cardiac history were more likely to refuse participation (OR=2.05; 95% CI: 1.39-3.02, p<.01), as were patients with non-cardiac medical history (OR=1.93; 95% CI: 1.22-3.07, p=.01). Also in a multivariable model, both were significantly associated with refusal (Table 2).

Psychological symptoms – For refusers who participated in cardiac rehabilitation, we had psychological screening data available. In this subgroup of refusers (N=38), no differences were observed in psychological symptoms in comparison with study participants (Anxiety: OR=1.03; 95% CI: .96-1.10, p=.38; Depression: OR=1.03; 95% CI: .97-1.10, p=.38; Type D personality: OR=1.02; 95% CI: .99-1.05, p=.27).

Characteristics of drop–outs

Most participants who quit the study did not give any reason for quitting (72%). The main reasons given for drop-out by the remaining patients were not being interested (11%), too much work to complete the questionnaires (7%), being too ill or disabled (6%), or being too emotionally distressed (3%) (Figure 1). Demographics, clinical risk factors, medical history, psychological symptoms, and information regarding prognostic factors are displayed in Table 1.

Demographics – Univariate analysis showed that older patients were more likely to drop out than younger patients (OR=1.02; 95% CI: 1.01-.03, p<.01), as were women (OR=1.66; 95% CI: 1.26-2.18, p<.01), and patients who were single (OR=1.38; 95% CI: 1.01-1.88, p=.05). SES was not associated with drop-out. In a multivariable analysis, only female sex remained significantly related with drop-out (Table 2). For low SES, a trend was observed (Table 2).

Clinical risk factors – Univariate analysis showed that smokers were more likely to quit participation (OR=1.58; 95% CI: 1.20-2.07, p=.001). Diabetes, hypertension, and hypercholesterolemia were not associated with drop-out (all p-values >.40). In a multivariable analysis, smoking remained significantly associated with drop-out (Table 2).

Medical history – Univariate analysis showed that patients with non-cardiac medical history were more likely to drop out (OR=1.32; 95% CI: 1.01-1.73, p=.04). Cardiac history was not significantly associated with loss to follow up (p=.87). In a multivariable analysis, non-cardiac medical history was still significantly associated with drop-out (Table 2).

Psychological symptoms – No differences were observed in psychological symptoms at one month in study drop outs compared to participants (Anxiety: OR=1.02; 95% CI: .99-1.05, p=.15; Depression: OR=1.02; 95% CI: .99-1.05, p=.18; Type D personality: OR=1.01; 95% CI: .99-1.02, p=.34).

Association of refusal and drop–out with outcomes

In total, 470 participants (54%), 191 drop-outs (51%), and 64 refusers (43%) started with cardiac rehabilitation in hospital. Refusers started cardiac rehabilitation significantly less often than participants (OR=.64; 95% CI: .45-.91, p=.01). Drop-out was not associated with not starting cardiac rehabilitation in hospital (OR=.87; 95% CI: .68-1.11, p=.25). In a multivariable model, correcting for age and sex, refusal remained significantly associated with decreased likelihood of starting cardiac rehabilitation (OR=.69; 95% CI: .48-.99, p=.04).

In total, 48 participants (6%), 11 drop-outs (3%), and 14 refusers (10%) passed away during follow-up (Figure 2). Refusers showed a trend of increased mortality (10% vs. 6%) compared to participants (OR=1.78; 95% CI: .95-3.32, p=.07), while drop-outs had a lower risk of death (3% vs. 6%) than participants (OR=.51; 95% CI: .26-1.00, p=.05). Compared to patients

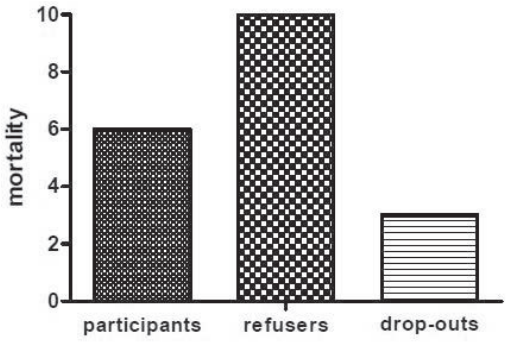

Figure 2. Mortality percentage for participants, refusers, and drop-outs.

who initially decided to participate (participants + drop-outs), refusers had a significantly higher risk of death (10% vs. 5%; OR=2.09; 95% CI: 1.14-3.85, p=.02).

DISCUSSION

The aim of the current study was to investigate the role of demographic, disease-related, and psychological factors in refusal and drop-out among patients with coronary artery disease in a prospective cohort study (THORESCI). We also examined whether these three groups were differentially associated with outcomes. Important differences between the groups were found with respect to demographics, disease-related factors, participation to cardiac rehabilitation, and mortality.

We found that patients who refused study participation were older than participants, had a lower socio-economic status, were more often smokers and experienced a larger burden of illness. Furthermore, refusers participated less often to cardiac rehabilitation as compared to study participants and dropouts, independent of age and sex. They also showed increased mortality compared to participants. This increased mortality may partly be explained by the higher prevalence of cardiovascular risk factors and increased illness burden. These findings are in line with previous work showing more unfavourable health behaviors, elevated moribidity and mortality among refusers than in study participants (20).

In drop-outs, also a higher prevalence of cardiovascular risk factors was found, including increased levels of smoking, and a larger burden of illness. However, drop-outs had a lower mortality risk than participants, which is in contrast with previous studies (13, 14). This discrepancy may be explained by the fact that patients who dropped out from the THORESCI study were more often women, who have a substantially lower mortality rate than men (21), while in previous studies no such sex differences between drop-outs and

parcitipants were observed (13, 14). However, compared to patients who initially decided to participate (participants + drop-outs), study refusers had a significantly higher risk of death, which is in line with previous work (12, 13).

In a subsample of refusers and drop-outs, information about psychological symptoms was available. We did not find any differences between the groups regarding psychological symptoms. This is in contrast with a previous study demonstrating higher levels of depressive symptoms in refusers than in participants (22). Importantly, the fact that in refusers we only had information about psychological symptoms when they participated to cardiac rehabilitation in hospital may partly explain this finding. We had no information from patients who refused both participation to THORESCI and to cardiac rehabiliation in hospital. However, this group represents an important part of the whole refusing patient group. Possibly, these patients are characterized by a more general form of uncooperativeness, e.g., with respect to following advice on adequate health behaviors such as smoking, which may be the consequence of specific patient characteristics such as psychological factors. It could also be that patients with higher levels of avoidance, inhibition, or shyness may not choose to particpate in a study that asks to disclose emotions, as was found in a previous patient-partner study (17).

Our results further demonstrated that refusers and drop-outs were characterized by more cardiovascular risk factors, including a lower socio-economic status, smoking, and a larger burden of illness. This relates to the "health gap", which states that an individuals' socio-economic position directly affects health (23). The lower one's position on the social scale, the lower one's survival risk and the worse one's health will be (23). Individuals at the lowest position on the social scale may be the ones that are the most in need. At the same time, women in the lower economic classes are worse off than men (23). Similarly, PCI patients that both refuse to participate to cardiac rehabilitation and to THORESCI may be the patients suffering the most from psychological and somatic symptoms.

To the best of our knowledge, we were the first to explore demographic, disease-related, and psychological factors in both refusers and drop-outs among patients with coronary artery disease in a prospective cohort study, which is a major strength of the study. However, there are also limitations that must be acknowledged. First, THORESCI is a single-center study, recruiting patients from a single mixed urban-rural area. Areas with a more metropolitain character may have a different ethnic, or socio-economic composition. Second, information about psychological symptoms was only available in a subsample of refusers and drop-outs. Moreover, during cardiac rehabiliation, anxiety, depression, and Type D personality were assessed in an interview by phone, which may increase patients' tendency to give socialy desirable answers.

The results of our study have important research and clinical implications. Usually, participation rate is reported in studies, while information about and comparison with

refusers and drop-outs are rarely provided. Our findings highlight the importance to consider possible bias that may affect participation and completion rate, as well as the projected results. It is thus important to report any data that compares refusers with participants and participants with dropouts, so that selection bias may be gauged. To get a better insight, it may be helpful to ask patients who refuse study participation for permission to extract data from their hospital medical records, as we did in THORESCI. From a clinical perspective, our results suggest that study refusal may reflect a prognostic risk factor for mortality post-PCI. It may be particularly important that inclusion for studies or cardiac rehabilitation is performed by a supportive person, who may make the patient feel more comfortable in participating. Emphasizing individuality and confidentiality in answering questions may also be important.

In sum, a possible selection-bias occurred in the current study, as study refusers and drop-outs differed systematically on some demographics and disease-related factors. This was translated into a poorer health outcomes, as there were differences in the mortality risk of refusers versus participants. The current findings suggest we lack a group of patients who are at increased risk for poor health. Therefore, we conclude that results from survey studies examining the association between psychosocial factors and health outcomes may underestimate the effects, as a healthier sample is participating than is present in the real life population. In future prospective studies, attention should be paid to this selection-bias, e.g., by designing targeted recruitment strategies, and its possible impact on study results and implications should be discussed. Future work is needed to further examine the importance of psychological differences between participants, refusers, and drop-outs.

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Chapter 8

General discussion

BACKGROUND AND AIMS OF THE DISSERTATION

Despite improved treatment options such as percutaneous coronary intervention (PCI), coronary artery disease (CAD) still is a long-term chronic condition that puts a high burden on patients. There is substantial heterogeneity in PCI patients' health-behaviors (e.g. maintaining a healthy lifestyle, adherence to treatment regime and cardiac rehabilitation) and patient-reported outcomes (physical and psychological symptoms) after treatment. Part of this heterogeneity may be explained by individual differences in psychosocial functioning. Based on the existing literature, a large number of psychosocial factors are known to affect health behaviors and patient reported outcomes in CAD patients. These psychosocial factors include positive and negative social factors, emotional symptoms, but also more stable characteristics such as personality and coping traits. However, it is still unclear how specific combinations of psychosocial factors, or *psychosocial profiles*, influence health-behaviors and affect patient-reported outcomes.

Several international cardiology workgroups from e.g. the European Society of Cardiology (ESC) and the American Heart Association recommend a "*routine screening for CAD patients' psychosocial profile*" because this may initiate sooner appropriate personalized care (1-3). However, there is substantial discussion on the value of screening, as studies examining depression screening have not yet reported improved CAD outcomes (4-8). A reason to explain these inconsistent findings may be that these studies only included one single psychosocial factor instead of patients' complete psychosocial profile.

The aim of this dissertation was to explain heterogeneity in patient-reported outcomes of PCI patients, through identifying intra-individual psychological profiles by applying a person-centered approach. We aimed to identify groups of individuals who share particular attributes or show similar scoring "profiles" (9, 10), which capture unique patient information that is not well covered by the use of multiple isolated trait scores (11). Person-centered techniques assume that the population is heterogeneous with respect to how specific predictors operate on outcomes and try to understand these patients' behavior from their individual characteristics. Throughout the manuscript we used different types of measures, i.e. the ESC screening interview, standardized questionnaires, and different types of psychological constructs to examine the within-person clustering.

We examined the psychometric properties of the ESC screening interview, in order to use the screener to identify latent multidimensional screening profiles. We also identified multidimensional latent psychological profiles based on a set of relatively stable psychological individual differences, including personality and coping traits. More specifically, we examined the sociodemographic, clinical and psychosocial correlates/characteristics of the extracted profiles, and the association of the profiles of stable psychological characteristics with multiple health-behaviors and patient-reported outcomes at follow-up. Furthermore, we

examined the incremental value of positive psychological constructs, including optimism, positive affect, and resilience as compared to negative psychological constructs, in order to improve our understanding of terms of emotional recovery patterns following PCI. Finally, representativeness of a study cohort is very important for the generalizability of study results. To examine potential selection bias, we compared the demographic, medical and psychological characteristics of study participants, drop-outs, and non-participants, and examined differences in medical treatment adherence and mortality between these three groups.

AN OVERVIEW AND DISCUSSION OF KEY FINDINGS

Screening for psychosocial profiles

In the 2012 guidelines of cardiovascular prevention, the ESC suggested a brief psychosocial screening interview that can be used during a physician's clinical contact (2). Its focus is on the seven psychosocial constructs with the most solid evidence for being a risk marker: depression (12) and anxiety (13), perceived work and marital stress (14), hostility (15), lower socio-economic status (16), lack of social support (17), and Type D personality (2). We examined the psychometric properties of the ESC screening instrument in a real-world CAD patient sample (*Chapter 2*), by examining internal, construct, and predictive validity. Factor analysis resulted in five separate constructs of psychosocial stress within the screener (Emotional distress, Work stress, Hostility, Social resources, and Social stress), reflecting comorbidity and some overlap between the theorized seven components (2). Comparison of the ultra-short and summarized screening items to matching full psychometric instruments resulted in fair to moderate agreement for depression, anxiety, and Type D personality, slight to faire agreement for work stress and marital stress, but less than satisfactory agreement for hostility. Importantly, a positive screening result for depression, anxious tension, and Type D personality predicted angina and cardiopulmonary symptoms one year after PCI treatment, independent of baseline angina and baseline cardiopulmonary symptoms. Hence, despite the fact that the ESC screener was not sufficiently valid to reliably detect the presence of all predefined psychosocial factors, this reasonably valid interview may contribute to the search for a multidimensional and easy-to-use psychosocial screening instrument for cardiac patients as it enables the examination of profiles instead of single factors. Based on our findings, we made suggestions for a revision and further validation of this instrument, which are currently underway.

Variable–centered approach: Interrelation and underlying structure of multiple psychosocial variables

To date, most research on psychosocial factors in CAD patients is based on a variable-centered approach, which strives to group similar variables or "traits" together (9, 10). A variable-centered approach isolates psychosocial characteristics on which patients reliably differ, and studies their correlational structure, stability over time, and predictive validity for specific outcomes (11). Consequently, this approach is well suited for addressing questions that concern the relative contributions that predictor variables make to a specific outcome (10).

We used factor analyses to gain more insight in the underlying structure of the investigated psychosocial variables in three chapters. The ESC screening interview comprised five underlying principal components (*Chapter 2*): Emotional distress, Work stress, Hostility, Social resources, and Social stress. The emotional distress factor also appeared in the other chapters that examined sets of relatively stable personality and coping traits. In addition to negative affectivity/emotional distress, in *Chapter 4*, Active coping, and Inhibition were revealed as underlying factors, while in *Chapter 5* negative affectivity was contrasted with positive affectivity, stressing the separate importance of positive and negative transient and stable psychological constructs as two distinct dimensions, instead of opposites of one continuum.

Overall, our data showed that different psychological and social variables may reflect different psychosocial domains. These findings indicate the importance of assessing multiple psychosocial components instead of one single factor in CAD patients. This is in line with the ESC who recommends multidimensional psychosocial risk factor assessment, using clinical interview or standardized questionnaires to identify possible barriers to lifestyle change or adherence to medication in CAD patients (18).

While we used different types of measurement instruments (i.e. ultrashort ESC screening interview vs. full-length standardized questionnaires), assessing different kinds of factors (i.e. transient emotional symptoms vs. relatively stable traits or cognitions vs. behaviors), all factor analyses revealed a Negative affect component. Both the Emotional distress component in *Chapter 2* and the Negative affectivity component in *Chapter 4* reflect the Negative affectivity construct (part of the prototypical Type D personality). Negative affectivity is an important personality correlate of psychiatric disorders, as it is highly related with symptoms and diagnoses of both anxiety and depression (19). This construct is a general trait of somato-psychic distress, which is expressed through a broad range of negative mood states and somatic complaints (20). Furthermore, there was overlap between the Emotional distress component in *Chapter 2* and the Negative constructs component in *Chapter 5*. These two components both comprised depression and anxiety. This supports previous findings showing high comorbidity between these psychological symptoms (21).

In accordance with the original Type D personality construct, Social inhibition loaded on different factors in *Chapters 2* and *4*. The Social stress component, which is identified in *Chapter 2*, is close related to the Inhibition component identified in *Chapter 4* (partly overlapping constructs). In *Chapter 2*, Social Inhibition clustered with social isolation and in *Chapter 4* with introversion and social interaction anxiety. The overlap between social inhibition and social interaction constructs is in line with previous work (22).

Positive psychological constructs reflecting patients' resources, including optimism and positive mood, clustered in a separate component, as were active coping styles (*Chapter 4*), representing a behavioral component, separate from emotion-focused coping, which is characterized by focusing on negative and distressing emotions that a stressful situation has caused (e.g. worrying, getting upset) (23). Another conclusion, which can be drawn from Chapter 2, is that psychological and social variables belong to different domains.

In sum, we detected a clear set of underlying psychosocial factors that may be of importance for health-related behavior and patient-reported outcomes in CAD patients after their treatment (Figure 1). Multiple variables regarding negative feelings cluster within one

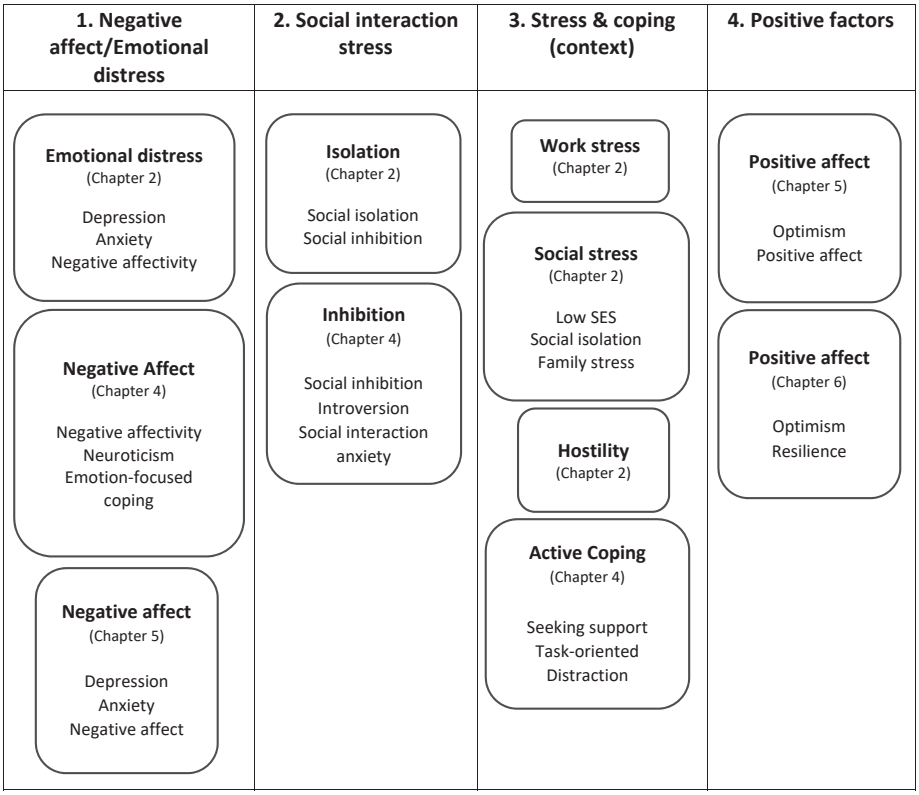

Figure 1. Interrelation and underlying structure of the investigated psychosocial variables.

domain, while variables regarding social interaction/social stress represent another domain. Moreover, we found that positive and negative psychosocial factors should be considered two separate dimensions. Finally, variables reflecting patients' behaviors and context related stress represented different components.

Person–centered approach: Multiple psychosocial profiles

While a variable-centered approach provides information about the trait structure, stability, and validity for an average person in the sample (11), information about the patient-specific intra-individual organization of psychosocial processes and behavior is neglected. In contrast, a person-centered approach, where the unit of analysis is the patient, studies individual psychosocial patterns or profiles. These profiles capture unique patient information that is not well covered by the use of multiple isolated trait scores (11).

In this dissertation multiple intra-individual psychological and social profiles were identified, which were linked to demographic, behavioral, psychological, and medical characteristics in *Chapter 3* and *4*, and to predict health-behaviors (treatment adherence and participation to cardiac rehabilitation) and patient reported outcomes (psychological symptoms) in *Chapter 4*.

Irrespective of the used measurement instrument (i.e. ESC screener vs standardized questionnaires), a *Low distress* profile and a *High distress* profile were identified (*Chapters 3* and *4*). The *Low distress* profiles represented patients reporting minimal psychological symptoms, while the *High distress* profiles represented patients with overall elevated levels of psychological symptoms. Moreover, compared to the other profiles, both *High distress* profiles were associated with higher levels of psychological symptoms, immediately after PCI treatment (*Chapter 3*) or after six months (*Chapter 4*). The *High distress* profile in *Chapter 3* was associated with younger age, unhealthy behaviors (smoking, sedentary lifestyle), and more often had a psychiatric history as compared to the other profiles. Patients with a *High distress* profile in *Chapter 4* were more often single, employed, and showed poor treatment adherence (general and cardiac rehabilitation) at follow-up.

Patients in both *High distress* profiles (*Chapters 3* and *4*) were characterized by the prototypical Type D personality profile (combination of Negative affectivity and Social inhibition). Type D personality has previously been associated with emotional problems and poor treatment adherence after a coronary event (24, 25). However, the *High distress* profiles may be considered as an example of co-occurring and inter-correlating risk markers that reflect vulnerable personality characteristics (e.g. Type D personality), unhealthy behavior and suboptimal social environment (e.g. being single) (26). The combination of Type D personality, being single, and being employed might, be a more accurate predictor of emotional symptoms at follow-up than a single psychosocial factor (26).

Furthermore, we identified two different coping profiles among CAD patients. The *Active coping* profile was characterized by patients who seek social support, distraction, and use task-oriented strategies to deal with stressful situations. Moreover, patients with an *Active coping* profile were more often unemployed. At follow-up, the *Active coping* profile was associated with increased levels of emotional symptoms as well as positive mood. This may be explained by an increased awareness of the own mental state regarding both positive and negative emotions. In fact, positive and negative psychological constructs should not be considered opposites of one continuum, but rather should be interpreted as two independent and uncorrelated dimensions (*Chapter 5*).

Patients with a *Passive coping* profile have the tendency to take a passive stance. While the *Active coping* profile was determined by high Negative affectivity and low Inhibition, the *Passive coping* profile was determined by low Negative affectivity and increased introversion. Patients with a *Passive coping* profile more often had a partner and were more often retired. Patients with a *Passive coping* profile did not seem to suffer from emotional problems. The combination of being married and being retired may partly explain the decreased risk for emotional problems at follow-up (27). Furthermore, they displayed a decreased level of positive mood and were less likely to participate in cardiac rehabilitation, which might be explained by the fact that they have the tendency to take a passive stance (23).

With respect to the social profiles, we identified a *Low chronic stress* profile and a *High work stress* profile (*Chapter 3*). The *High work stress* profile comprised blue collar workers lacking control over how to meet the demands at work with a disrupted effort-reward balance. Patients with high work stress were younger and consumed alcohol more frequently as compared to the *Low chronic stress* profile. In stressful situations, patients with this profile tended to avoid stressors (e.g. trying to sleep, shopping or watching television to cope with stressful situations). This profile was more common among patients who had a first-time, often acute, event and no cardiac or non-cardiac comorbidities. Compared to the other psychological classes, patients in the *High hostility* subgroup were most likely to have a *High work stress* profile, although overlap was limited to a quarter of the total study.

Sex differences

Two other profiles that emerged are informative for gender specific medicine. While women were more likely to have a *High tension* profile, characterized by high anxious tension, low to moderate anxious worry, and depressive symptoms, men more often had a *High hostility* profile, characterized by high levels of anger and annoyance, and moderate levels of anxiety and social inhibition (*Chapter 3*). Women with a High tension profile had an increased psychological burden. I.e., patients in this subgroup reported high negative affectivity, more early adverse life-events, a psychiatric history, and higher levels of depression and anxiety

immediately after PCI treatment. Men with a *High hostility* profile reported high negative affectivity and psychiatric history.

These findings are in line with our results considering emotional recovery profiles, showing that women were more likely to be in recovering and persisting depression/anxiety profiles as compared to men. This indicates that female patients were more likely to have preexisting substantial depressive or anxiety symptoms, or have an immediate emotional response that subsided over the first month after PCI as compared to men (*Chapter 6*).

In addition to the psychological differences men and women also differed in behavioral aspects. Women were more often single, maintained a sedentary lifestyle, and tended to seek social support in stressful circumstances (*Chapter 3*). Earlier studies have shown similar gender differences in cardiovascular patients. It was, for example, shown that hostility predicts the presence of cardiovascular diseases in men, while anxiety predicts cardiovascular diseases in women. Furthermore, it was found that psychological symptoms, such as depression, are more common among women than men (28), and that associations between anxiety (e.g. tension) and cardiovascular diseases were stronger in women than in men (29).

Additionally, the current results confirm the important difference between different types of anxiety. When comparing the *High hostility* profile with the *High tension* profile, substantial differences exist in scores on anxious tension, but not on anxious worry. Previous work already accentuated the difference between cognitive (e.g. worry) and somatic (e.g. tension) anxiety symptoms, both contributing to the pathophysiology of cardiovascular diseases through different psychobiological pathways (30). Our findings add that cognitive and somatic anxiety symptoms are not only associated with different pathways affecting cardiovascular health, but may also represent distinct underlying patient groups, both associated with a specific set of characteristics (31).

In sum, considering psychosocial risk markers for CAD patients, we highlight the importance of assessing sex differences.

Positive psychological factors

Positive psychological constructs (positive mood and optimism) may be of incremental value to negative psychological constructs (depression and anxiety) in predicting patients' treatment adherence. We found that higher optimism predicted better general treatment adherence six months after PCI treatment, independent of demographic, clinical, and negative psychological covariates (*Chapter 5*).

Chapter 6 examined the association of relatively stable positive psychological constructs (optimism and stress resilience) with distinct emotional recovery profiles (resilient, immediate, delayed, and persisting) after PCI treatment. The results demonstrated that both optimism and stress resilience were highly associated with a resilient depression and

anxiety response (low scores on baseline, one, and six months after PCI treatment). Higher optimism was protective for most adverse post-PCI depression and anxiety response profiles, while pessimism was associated with persisting psychological symptoms (high scores on baseline, one, and six months after PCI treatment for depression and anxiety) and delayed emotional responding. Lack of stress resilience predominantly had added value in predicting the persisting profiles.

In sum, our findings indicated that it is of major importance to highlight both positive and negative psychological functioning in patients with CAD. This is in line with the patient-centered cumulative complexity model, according to which outcomes can be affected by a combination of patient capacity and patients' workload of demands (32). This model highlights that patient capacity comprises both patients' resources (e.g. psychological well-being) and patients' limitations (e.g. psychological complaints). Accordingly, increasing positive affect, resilience and optimism.

HOW TO RECRUIT THE MOST ELUSIVE PATIENTS AND HOW TO KEEP THEM IN THE STUDY

All studies described in this dissertation have been based on the Tilburg Health Outcomes Registry of Emotional Stress in Coronary Intervention (THORESCI) cohort. As are many of the studies focusing on the association between psychosocial factors and clinical course in coronary artery disease, THORESCI has a prospective cohort design. Importantly, when specific patient characteristics (e.g., demographics, disease severity, psychological factors, comorbid diseases) interfere with patients' motivation for study participation or completion, this design may be sensitive to selection-bias (33). Systematic differences between study participants and patients who refuse to participate or patients who are lost to follow-up due to attrition may threat internal validity and generalizability of the study findings (33, 34).

In the current dissertation, we found important differences with respect to demographic, disease-related, and psychological patient characteristics of those who refused to participate ("refusers"), those who quit participation during follow-up ("drop-outs"), and study participants (*Chapter 7*). Both drop-outs and refusers were more often women and had a lower socio-economic status as compared to participants. In both groups, also a higher prevalence of cardiovascular risk factors was observed, including increased levels of smoking and a larger burden of illness. Moreover, refusers were older than participants. They also started less often with cardiac rehabilitation as compared to study participants, independent of age and sex. Furthermore, compared to patients who initially decided to start (participants + drop-outs), study refusers had a significantly higher risk of death. These findings were in line with previous work that focused on non-participants and drop-outs to prospective cohort studies (33, 35-37). The phenomenon that healthy persons are more likely

to participate or complete studies as compared to persons with, diagnosed or undiagnosed existing disease is also described as the "healthy volunteer effect" (38-44).

Moreover, our findings relate to the "health gap", which states that an individuals' socio-economic position directly affects health (45). The lower one's position on the social scale, the lower one's survival risk and the worse one's health will be (45). Individuals at the lowest position on the social scale may be the ones that are the most in need. At the same time, women in the lower economic classes are worse off than men (45). Similarly, PCI patients that both refuse to participate in THORESCI and to start with cardiac rehabilitation may be the patients suffering the most from psychological and somatic symptoms. Another barrier to recruitment and retention may be the general mistrust of the medical/scientific community among minorities (46).

To minimize a potential health gap, in both scientific research and in cardiac rehabilitation programs, emphasizing individuality and confidentiality in answering questions are important. Previous work recognized the role of healthcare professionals in increasing referral and participation rates to cardiac rehabilitation (47, 48). Recently, an intervention that aimed to increase participation to cardiac rehabiliation by providing additional written and oral explanations on the programs' benefits and eligibility has shown to be effective (49). Therefore, iinclusion for studies or cardiac rehabilitation should be performed by a supportive person, who clearly communicates and makes the patient feel comfortable in participating (50). Our research assistants (psychologists in training) approached each patient individually, and made an effort to connect with the patient before asking for participation. Four times a year, participants received a newsletter informing them about the research project and the results. Educating patients about the impact of psycholocial factors and health behaviors on disease progression might postively affect patients motivation to complete paticipation to THORESCI. When patients did not complete their questionnaires on time, they were called multiple times by one of the research assistants. Nevertheless, 30% refused participation and 30% of the participants was lost to follow-up. Additional strategies to minimize refusal and attrition among patients with a low socio-economic status that may be considered include highlighting the research hypothesis that are directly relevant for them and to focus on providing a direct benefit for participants, such as cash reward (50).

INSIGHT IN HETEROGENEITY IN HEALTH BEHAVIORS AND PATIENT–REPORTED OUTCOMES AFTER PCI

After percutaneous coronary intervention, there is substantial heterogeneity in patients' health-behavior and in patient-reported outcomes such as physical and psychological symptoms, which may be due to individual differences in demographic, clinical, and psychosocial characteristics. Bandura's social-cognitive theory, which is one of the most

comprehensive health behavior models thus far, may give more insight in the heterogeneity in health behavior and patient-reported outcomes after PCI (51). This model considers patient-reported outcomes as a result of a dynamic interaction between three main constructs: environment, patient, and behavior (51). Interactions between these constructs may occur in various ways.

After PCI, which can be considered an external influence on the patient (environmental variable), both patients' knowledge about CAD (e.g., health risks) and patients' personal characteristics (i.e. 'self-influences') may facilitate or inhibit certain health-related behaviors (e.g., participation to cardiac rehabilitation or treatment adherence) (52). Self-influences that may interfere with PCI patients' health-related behavior include social factors, emotional symptoms, and relatively stable psychological characteristics.

Based on the existing literature, a large number of psychosocial factors are known to affect health behaviors and patient reported outcomes in CAD patients. However, in most situations, these factors do not occur in isolation from one another but tend to cluster in the same individuals and groups. With this dissertation we gained more insight in how specific combinations of psychosocial factors, or *psychosocial profiles*, induce certain health-behaviors such as treatment adherence and participation to cardiac rehabilitation and how these combinations affect patient-reported outcomes after PCI. With a variable-centered approach, we identified four important underlying components, including Negative affect/ Emotional distress, Social interaction, Stress & coping, and Positive affect. These components reflect social factors, emotional symptoms, but also more stable characteristics that often tend to cluster in CAD patients. Additionally, we examined how these components were related with health-behaviors and patient reported outcomes. Moreover, with a person-centered approach, we identified multiple multidimensional psychosocial profiles. These profiles reflect subgroups of patients who share particular attributes and capture unique patient information that is not well covered by the use of multiple isolated trait scores. We also studied the association between these profiles with health-related behaviors and patient-reported outcomes.

LIMITATIONS AND STRENGTHS OF THE DISSERATION

A number of limitations must be acknowledged. The current knowledge from this dissertation is based on information from self-report measurements, a face-to-face psychosocial screening interview, and patients' medical records. Data on psychosocial functioning were obtained from self-report questionnaires and the screening interview as proposed by the ESC. While both instruments are easy to use and low-cost methods, they may be sensitive to social desirability and not reflect actual psychological functioning and behaviors. Regarding

personality traits, we only included factors that are related to neuroticism and introversion, while other traits that may be related to patient-reported outcomes and health-behaviors (e.g. conscientiousness) were not examined. Data on health-behaviors, such as treatment adherence and participation to CR were derived from self-report questionnaires and patients' medical records. While these measures give a clear view of patients' general treatment adherence and whether patients started with CR in hospital, more specific information regarding these health behaviors was not taken into account. Participants who started CR may for example differ in the number of sessions they attended. Moreover, they may have participated in different modules (e.g. both the physical and psychological module vs. only the physical module). With respect to general treatment adherence, we did not incorporate potential differences in treatment instructions that patients received or in cardiologists' attitudes towards treatment (e.g. regarding benefits of cardiac rehabilitation).

Second, while we included a broad set of psychosocial measures, the dependent variables only included health-behaviors and patient-reported outcomes at a relatively short follow-up period. In the current sample, it was impossible to examine the association between psychosocial functioning and other, longer-term outcomes during follow-up such as cardiac events, because the event prevalence was <2%. This is in line with recent findings showing that six month mortality after myocardial infarction has decreased considerably over the past two decades (53).

Third, THORESCI is a single-center study in the Netherlands and only comprised CAD patients, of which 95% was Caucasian. This is expected from a PCI sample in the Netherlands, but this makes it impossible to generalize the study results to other ethnic groups or other cardiac samples, such as patients with heart failure or atrial fibrillation.

Key strength of the present study is its clearly defined and relatively large patient population, representing an important part of the real-world population of patients with CAD. This provided the opportunity to evaluate the pre specified hypotheses with well-designed statistical models. A second important strength was the prospective study design, which made it possible to examine associations between psychosocial functioning and outcomes during follow-up. Another strength is the psychosocial multidimensionality of the study, comprising multiple transient and relatively stable positive and negative psychological and social characteristics. Psychosocial functioning was assessed by the ESC screening interview and widely-used reliable measurement instruments. We also used different approaches in this dissertation, including both variable-centered and person-centered perspectives.

IMPLICATIONS AND CONSIDERATIONS FOR CLINICAL PRACTICE AND FUTURE RESEARCH

In the current dissertation, we detected a clear set of psychosocial components, each reflecting a distinct domain of psychosocial constructs that tend to cluster in CAD patients: Negative Affect, Social Interaction Stress & coping, and Positive affect. Additionally, this dissertation reveals a richness of psychological influences captured in patients' psychosocial profiles that may add valuable information which never can be gauged by examining single factors alone. These findings help to explain the large degree of heterogeneity in health-behaviors and patient-reported outcomes following PCI. In future research examining the association between psychosocial functioning and outcomes after treatment, it might be useful to incorporate the identified psychosocial components and to assess patients' psychosocial profiles instead of single factors.

The current results may enhance personalized medicine, which aims to individual care according patients' unique characteristics (54). Personalized medicine implies a tailored approach, offering a therapy that is effective for each individual, reducing risks and avoiding unnecessary treatments or diagnostic interventions (54). Initial concepts of personalized medicine focused heavily on genetic markers and application of risk stratification based on clinical, biochemical, imaging, and/or genomic markers is already used to tailor therapy (55). However, up to now, individual characteristics such as social and environmental context, and psychological factors were mostly left out of the equation. The findings of the current dissertation may be helpful in tailoring treatment for specific subgroups of PCI patients, for example, in developing interventions to target specific subgroups. By installing automatized queries looking for combinations of determinants that are relevant to the psychosocial profiles, clinicians may ask patient-tailored follow-up questions to be able to make a tailored referral.

A revised version of the ESC screening interview may be useful to tailor treatment in clinical practice. In THORESCI, implementation of the 15-item psychosocial interview, immediately after treatment or 1 month later (in acute PCI patients), was relatively easy to achieve. This screener is a simple, easy-to-use, and low-cost instrument. However, screening is only useful when appropriate psychological care supports are in place (3, 56). To apply this in clinical practice, for example, by nurses or cardiologists, basic guidelines from a mental health expert are needed. In a stepped care protocol (56), a positive screen on the (revised) ESC screening instrument in step 1 needs to be followed by more in depth diagnostic assessments by skilled professionals. Next, tailored management can be arranged, for example, in the context of cardiac rehabilitation, such as a consult with a specialized medical psychologist to correctly determine absence or presence of psychosocial problems, and install treatment if necessary. Importantly, in the current study, we chose to administer

the interview in an early stage (i.e. immediately after coronary treatment or 1 month later), and validity of the screening interview at other time points, e.g. during stable phases of the disease such as one year after treatment, should be investigated in future work.

In addition to screening for psychosocial symptoms, it may be considered to also identify patients' resources, such as optimism or resilience, and coping styles. Determining patients' resources may take place in a second step, after screening for psychosocial symptoms. This is in line with the *Cumulative Complexity Model*, according to which health-behavior and patient-reported outcomes result from a combination of *patient capacity* and *patients' workload of demands* (32). The model highlights that *patient capacity* comprises both patients' limitations (e.g., psychological complaints) and patients' resources (e.g., psychological well-being) (32). Accordingly, enhancing patients' resources may be a useful target for intervention, because increasing positive psychological functioning could enhance patients' capacity, which should in turn induce better self-care (32). Additionally, assessing patients' resources may be helpful in determining which patients need more attention in the recruitment process for participation to cardiac rehabilitation. For example, patients with a *Passive coping* profile, who did not seem to suffer from emotional problems, will probably not have a positive ESC screen, while their passive stance might prevent them from participation to cardiac rehabilitation.

Furthermore, the clinical course of CAD varies considerably between ethnic groups. Compared to Caucasians, South Asians and sub-Saharan Africans have a higher risk on adverse outcomes, while Chinese and South Americans have a lower risk (57, 58). It is also known that there are important sex-differences in health-behaviors. CR adherence, for example, is significantly lower among women than men (59). Therefore, future research may include larger samples of women and different ethnic groups. In the current sample, it was also impossible to examine the association between psychosocial functioning and other, longer-term outcomes, such as cardiac events, because the event prevalence was <2%. This low event prevalence is in line with recent findings showing that six month mortality after myocardial infarction has decreased considerably over the past two decades (53). However, for a further determination of heterogeneity in the prognosis of patients with CAD, it may be interesting to look beyond six-month outcomes and examine the association between the profiles with longer term and other clinical outcomes. As THORESCI is an ongoing study, in the future we will be able to report on longer term outcomes.

CONCLUSION

With this dissertation we gained more insight in how specific combinations of psychosocial factors, or *psychosocial profiles*, induce certain health-behaviors such as treatment adherence and participation to cardiac rehabilitation and how these combinations affect

patient-reported outcomes after PCI. These multidimensional profiles incorporate transient variables, more stable psychological characteristics, and chronic stress constructs. Moreover, it is of major importance to highlight both patient's resources (e.g. psychological well-being) and patients' limitations (e.g. psychological complaints). This knowledge expands existing theories focusing on health-related behavior (e.g. treatment adherence and cardiac rehabilitation participation) and patient-reported outcomes (e.g. mental and physical well-being). Therefore, the current findings may be helpful in tailoring CAD patients' treatment after PCI. Future research is needed to examine the association of these psychosocial profiles with other, longer term outcomes.

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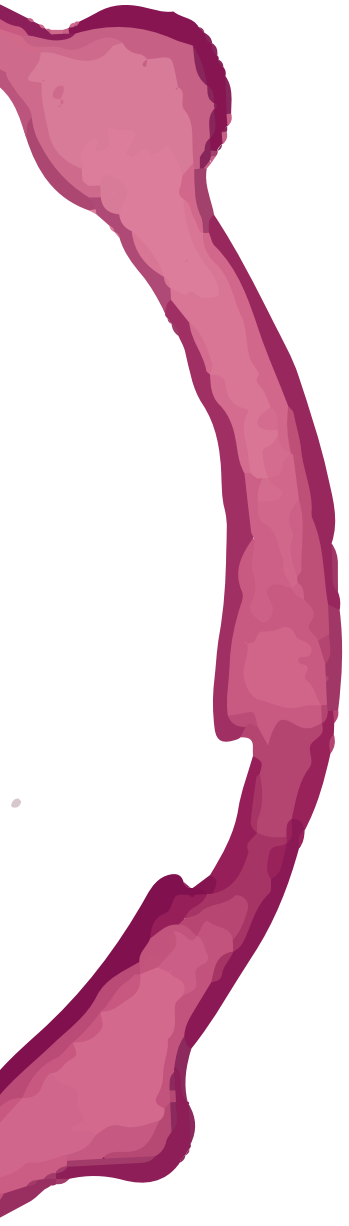

Chapter 9

Acknowledgements/Dankwoord
Publications
About the author

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PUBLICATIONS

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